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The Association Of Changes In Cardiorespiratory Fitness With Changes In Cardiometabolic Risk Factors

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THE ASSOCIATION OF CHANGES IN CARDIORESPIRATORY FITNESS WITH
CHANGES IN CARDIOMETABOLIC RISK FACTORS

by

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DEDICATION

To my Lord and Savior, Jesus Christ, my parents, Charles and Ardeth, my brother, Ryan, and my family and friends who have been a constant source of support, encouragement, and love. *2 Peter 3:18*

In loving memory of Dr. Raja Fayad, who played an inspirational role in the pursuit of my doctoral degree.

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As I reflect on my time at USC, I am reminded of numerous opportunities that have not only prepared me for my career as a scientist, but also enriched my life as a whole. I am forever grateful for the people that God introduced to my life during this journey who have provided encouragement, support, laughter, kindness, mentorship, and friendship. You all fill a special place in my heart.

To my committee members, I continue to be at a loss for words that truly encompass my gratitude for all you have done for me along this journey. Dr. Blair and Dr. Durstine, your influence in my life extends far past the realms of teaching and research. I consider you to be family and appreciate all of the opportunities and unwavering support that you have provided over the past several years. Dr. Shook, you have been there for me since day one of graduate school. I am thankful that my time at USC has come full circle with you being a part of my dissertation committee. Dr. Drenowatz, your guidance throughout my time as a doctoral student helped shape my abilities to become an exercise scientist, and I am glad you were able to be a part of this process even after your move back home. Dr. Sarzynski, thank you for your countless hours dedicated to helping me. You enabled my initial research idea to grow into an outstanding project. The cascade of opportunities from your mentorship has led me to the next step in my journey: beginning my dream postdoctoral fellowship at Duke University. I cannot wait to see what happens next!

ABSTRACT

Cardiorespiratory fitness (CRF) is well established as having a strong inverse association with numerous cardiovascular disease (CVD) risk factors and mortality. As CVD remains the number one cause of death in America, the detrimental effects of low CRF present a substantial health threat. The studies presented in this dissertation syndicate both epidemiologic and clinical data that will enrich the knowledge base regarding the magnitude of change in CRF in relation to CVD risk factors.

Recently, the American Heart Association established a new construct termed ideal cardiovascular health (CVH), which is characterized by seven metrics known as Life's Simple 7. The concept emphasizes seven positive health factors and behaviors. The promotion of achieving and retaining these metrics at an ideal level serves to improve CVH and decrease public health burden and CVD mortality. This first study of this dissertation found that higher levels of CRF are strongly associated with better CVH profiles, which was demonstrated by individuals with moderate and high CRF exhibiting almost 11 and 40 times greater odds of having average or optimum CVH scores, respectively, compared to low fit individuals. Additionally, longitudinal analyses showed that improvements in CRF over time are associated with significant improvements in CVH score. These findings support the vital role CRF plays in public health efforts aiming to prevent the development of CVD and reduce CVD mortality risk.

Secondly, this dissertation investigated the responsiveness of CRF, as measured by maximal oxygen consumption ($\dot{V}O_{2max}$), and CVD risk factors following aerobic exercise intervention. Aerobic exercise interventions are used to increase CRF in order to help combat the detrimental effects of low CRF. However, relying solely upon group

mean changes can be misleading as considerable inter-individual variation exists in the ability to improve CRF and CVD risk factors to standardized interventions. This study is likely the first to assess the prevalence of $\dot{V}O_{2\max}$ responsiveness across 14 diverse exercise interventions. Although the exercise interventions produced significant mean increases in $\dot{V}O_{2\max}$, evaluation of individual changes in $\dot{V}O_{2\max}$ revealed that 34% of the total sample was considered low $\dot{V}O_{2\max}$ responsive. Within studies that employed multiple exercise interventions, a trend emerged. As exercise amount and intensity increased within studies, prevalence of low $\dot{V}O_{2\max}$ response decreased. The utility of these responsiveness cutpoints helps to provide a better understanding of the inter-individual variation in response to exercise training to enhance our ability to provide personalized exercise prescription for improved health and attenuated CVD risk.

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CHAPTER 1

OVERALL INTRODUCTION

Cardiorespiratory fitness (CRF) is well established as having a strong inverse association with numerous cardiovascular disease (CVD) risk factors and mortality.¹ As CVD remains the number one cause of death in America,² the detrimental effects of low CRF present a substantial health threat. Recently, the American Heart Association (AHA) launched a new primordial prevention approach called, “Life’s Simple 7” which emphasizes seven positive health factors and behaviors [blood cholesterol, blood pressure (BP), fasting plasma glucose, diet quality, physical activity (PA), smoking, and body mass index (BMI)]. The promotion of achieving and retaining these health metrics at an ideal level serves to improve cardiovascular health (CVH) and decrease public health burden and CVD mortality in the United States (U.S.).³ Despite the strong associations between CRF and each individual component of “Life’s Simple 7,” the associations between CRF and ideal CVH in adults cross-sectionally or longitudinally are currently unknown.

Aerobic exercise interventions are used to increase CRF, as measured by maximal oxygen uptake ($\dot{V}O_{2max}$), as an experimental approach in order to help combat the detrimental effects of low CRF. However, considerable inter-individual variation exists in the ability to improve CRF and CVD risk factors in response to regular exercise. Given the strong relationship between $\dot{V}O_{2max}$ and

cardiometabolic risk factors, identifying individuals who may not experience clinically significant gains in CRF with aerobic training (i.e., low $\dot{V}O_{2\max}$ response) is of great interest. The ability to identify individuals who respond unfavorably to an exercise intervention will facilitate adjustment of their exercise prescription to maximize clinically important health adaptations.

The studies of this dissertation syndicated both epidemiologic and clinical data to enrich the knowledge base regarding the magnitude of change in CRF and cardiovascular health markers. The relationship between changes in CRF and changes in ideal CVH profile were established by analyzing data from a large prospective, longitudinal study. Then, data from eight large exercise training studies comprised of 14 different standardized exercise interventions was utilized to assess the prevalence of low $\dot{V}O_{2\max}$ response and determine if $\dot{V}O_{2\max}$ responsiveness is related to concomitant changes in cardiometabolic risk factors. Thus, the purpose of these studies was to 1) identify the relationship between ideal cardiovascular health and CRF both cross-sectionally and longitudinally, 2) ascertain the prevalence of low $\dot{V}O_{2\max}$ response across several standardized aerobic exercise interventions, and 3) identify the relationship between $\dot{V}O_{2\max}$ responsiveness and changes in CVD risk factors across the aforementioned exercise interventions. The following aims were proposed to accomplish these goals.

Aim 1 evaluated whether ideal CVH as defined by AHA's 'Life's Simple Seven' is associated with CRF. In addition, the relationship between changes in CRF and changes in ideal CVH score over time was examined. These associations were

investigated in the Aerobics Center Longitudinal Study (ACLS), a prospective observational study where the participants underwent thorough medical examinations and maximal graded exercise testing to assess CRF at multiple time points. CRF as a continuous variable was quantified as treadmill time (mins) achieved during graded maximal exercise testing. Additionally, three CRF groups were created from age- and sex-specific quintiles based on previously established cutpoints of treadmill time: low (lowest 20%), moderate (middle 40%), and high CRF (upper 40%). For longitudinal analyses, change in CRF was categorized by grouping participants into categories of loss, stable, or gain, based on tertiles of change in CRF. The ideal CVH metrics comprising 'Life's Simple Seven' were used to create an ideal CVH score for participants in the ACLS. These metrics include seven positive health factors and behaviors: abstinence from smoking within the past year, ideal body mass index, physical activity at goal levels, consumption of a dietary pattern that promotes cardiovascular health, untreated total cholesterol (< 200 mg/dL), untreated blood pressure ($< 120/80$ mmHg), and the absence of diabetes mellitus and clinical CVD. Each of these ideal CVH metrics was classified as poor (value of 0), intermediate (1) or ideal (2). Ideal CVH was calculated by summing the scores across all seven categories, with each poor metric receiving no points, each intermediate metric receiving one point, and each ideal metric receiving two points. Participants were categorized based on their total ideal CVH score out of 14 possible points as follows: inadequate (0-4), average (5-9), and optimum (10-14). Change in total ideal CVH score was categorized by grouping participants

into categories of loss, stable, or gain, based on tertiles of change for longitudinal investigations. This study will provide valuable insight as to whether ideal CVH is associated with CRF and whether improvements in CRF over time are associated with beneficial changes in ideal CVH score.

Objective 1.1: To determine the cross-sectional association of ideal CVH with CRF

Hypothesis 1.1: We hypothesized that higher CRF, as a continuous variable, will be correlated with greater ideal CVH score. We also hypothesized that participants in the moderate to high categories of CRF will have increased odds for being in average or higher ideal CVH categories.

Objective 1.2: To examine the longitudinal association of changes in CRF with changes ideal CVH score

Hypothesis 1.2: We hypothesized that increases in CRF over time are associated with beneficial changes in ideal CVH score.

Aim 2 sought to identify cutpoints in order to define low $\dot{V}O_{2max}$ responsiveness. Using these cutpoints, prevalence of low $\dot{V}O_{2max}$ response across eight large exercise training studies that include 14 different standardized and supervised aerobic exercise interventions was assessed. Subsequently, Aim 2 investigated the relationship between changes in $\dot{V}O_{2max}$ and changes in cardiometabolic risk factors. Participants were enrolled in one of 14 exercise training programs that ranged from doses of 4-35 kcal·kg⁻¹·week⁻¹ (KKW); intensities of 50-85% $\dot{V}O_{2max}$; and durations of 20-35 weeks. Baseline and post-training $\dot{V}O_{2max}$ assessments

were completed via maximal graded exercise testing. Low $\dot{V}O_{2\max}$ response was defined in both absolute and relative terms based on technical error (TE) and coefficient of variation values derived from three repeatability studies in the HERITAGE Study. Results from this aim determined the association between $\dot{V}O_{2\max}$ responsiveness and concomitant changes in cardiometabolic risk factors [resting systolic blood pressure (SBP) and fasting insulin, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)]. This enhanced understanding will improve the ability to develop and adjust future exercise programming.

Objective 2.1: To identify cutpoints to define responsiveness of change in $\dot{V}O_{2\max}$ following standardized aerobic exercise interventions

Objective 2.2: To determine the prevalence of low $\dot{V}O_{2\max}$ response across multiple standardized aerobic exercise interventions

Objective 2.3: To examine whether exercise dose and/or intensity is associated with the prevalence of low $\dot{V}O_{2\max}$ response

Hypothesis 2.3: We hypothesized that greater exercise dose and intensity will yield lower prevalence of low $\dot{V}O_{2\max}$ response, with intensity playing a larger role in $\dot{V}O_{2\max}$ responsiveness.

Objective 2.4: To compare differences in changes of cardiometabolic risk factors between $\dot{V}O_{2\max}$ response groups

Hypothesis 2.4: $\dot{V}O_{2\max}$ responders will have greater beneficial changes in cardiometabolic risk factors compared to low $\dot{V}O_{2\max}$ responders.

Objective 2.5: To determine the distribution of low responses across all traits (CRF, resting SBP, fasting insulin, HDL-C, and TG)

Hypothesis 2.5: There will be participants with one or more low responses, however we hypothesize that no individual will be a low responder for all traits.

These studies are likely the first to evaluate the relationship between CRF and the AHA's ideal CVH score in adults. In addition, we will be one of the first to examine whether improving CRF relates to a positive change in ideal CVH score over time. Recent investigations have found that increasing numbers of ideal CVH metrics and scores are associated with more favorable future CVD outcomes.⁴⁻¹⁶ Thus, our study's examination of CRF's association with increasing ideal CVH score will provide meaningful insight for future investigations regarding CRF's role in public health efforts aiming to prevent the development of CVD.

We will also likely be the first to establish cutpoints to define $\dot{V}O_{2max}$ responsiveness by using a comprehensive and data-driven approach that is based on repeatability studies conducted in the HERITAGE study. Our innovative study design employed a large sample size that included multiple standardized and supervised aerobic exercise interventions. To date, no other study has evaluated the prevalence of low $\dot{V}O_{2max}$ response across diverse populations and varying exercise programs. As we move further into the era of personalized medicine, a better understanding of the inter-individual variation in response to exercise training will enhance our ability to utilize exercise as medicine and provide appropriate guidance to improve health and attenuate risk for cardiometabolic diseases.

CHAPTER 2

GENERAL METHODOLOGY

Aim 1

Aim 1 evaluated if ideal cardiovascular health (CVH) as defined by the AHA's "Life's Simple Seven"³ is associated with CRF (Objective 1.1). In addition, the relationship between changes in CRF and changes in ideal CVH score over time was examined (Objective 1.2).

Study Design

This study employed both cross-sectional and longitudinal analyses. A cross-sectional analysis examined if CRF is associated with ideal CVH. A longitudinal analysis was used to examine the relationship between changes in CRF and changes in ideal CVH score over time.

To address aim 1, data from the ACLS was utilized. The ACLS is a prospective observational study of participants who were self-, employer-, or physician-referred for an extensive medical examination at the Cooper Clinic in Dallas, Texas. The study investigated the health outcomes associated with physical activity and CRF levels. All participants received written and oral informed consent and the ACLS study has been reviewed and approved annually by the Cooper Institute's Institutional Review Board.

Study Population

This study included participants from the ACLS who completed at least two medical examinations by a physician after a 12-hour (hr) overnight fast between the years of 1987-1999. The medical examination was a complete preventive medical evaluation including physical examination, personal and family health history, questionnaires (demographics and health habits), anthropometry, resting electrocardiography, blood chemistry analyses, blood pressure, and a maximal exercise treadmill test. Health history questionnaires included: personal history of myocardial infarction, stroke, hypertension, diabetes, and cancer; parental history of CVD; smoking status, alcohol intake, and PA. Participants also completed a 3-day diet recall. Time between examinations ranged from 12 months to 11 years. Details of the examinations have been described elsewhere.¹⁷ Participants with complete data on CRF and all of the AHA's "Life's simple 7"³ health behaviors and factors (smoking, BMI, PA, dietary data, blood cholesterol, blood pressure, and fasting plasma glucose) were included. Participants were excluded if they had any form of CVD or cancer, or if they had abnormal findings on electrocardiography at baseline.

Measurements

Anthropometrics. Anthropometric measures were taken and BMI was calculated as weight in kilograms divided by height in meters squared. BMI values were classified as follows: normal (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), or obese (≥ 30.0 kg/m²). Resting blood pressure was measured by the auscultatory method with a mercury sphygmomanometer. To ensure

accuracy, two measures were taken and if the readings differed by more than 5 mmHg, then a third measure was taken and all the measures were averaged. Blood samples were taken from the antecubital vein after 15 to 20 minutes (min) of sitting. Concentrations of total cholesterol and fasting plasma glucose were measured by automated techniques.¹⁸⁻²⁰

Cardiorespiratory fitness. Maximal treadmill testing using a modified Balke protocol was used to assess CRF, which was defined as treadmill time in min, at baseline and during follow-up visits, as previously described.^{17, 21} Three CRF groups were created from age- and sex-specific quintiles based on the previously established cutpoints of treadmill time: low (lowest 20%), moderate (middle 40%), and high (upper 40%) CRF.¹⁷

Change in CRF as a continuous variable was calculated as the difference in treadmill time between the first two adjunct examinations and divided by the number of years between them. Annual change in CRF was used to define change in fitness because the intervals between the follow-up examinations varied among individuals in our cohort. Annual change in CRF was categorized by grouping participants into categories of loss, stable, or gain, based on tertiles of change in CRF. For example, a participant categorized in the low CRF group at baseline and increased to the moderate CRF group at follow-up would be categorized as gain in the CRF change groups.

Diet. Participants were asked to keep detailed records of everything they consumed over two pre-assigned weekdays and one weekend day for the 3-day dietary assessment. Written instructions on how to accurately describe foods and

portion sizes were given to each participant. Registered dietitians at the Cooper Clinic coded and analyzed the diet records using the Cooper Clinic Nutrition and Exercise Evaluation system. Achievement of the AHA diet goals were categorized as follows: 4.5 or more servings of fruits and vegetables per day, two or more 3.5 oz. servings per week of fish, shellfish, or other seafood, three or more servings per day of whole grains, and less than 1500 mg per day of sodium. Diet scores were assigned by giving a point for each diet goal met (i.e., consuming <1500 mg/day of sodium is one point) for a total possible score of four points.

Physical Activity. Participants completed a formerly validated questionnaire to assess leisure time PA over the past three months, which included type, frequency, and duration of activity. PA categories were created based on the responses to 10 specific activities: walking, jogging, running, treadmill exercise, cycling, stationary cycling, swimming, racquet sports, aerobic dance, and other sports related activities. The intensity of the activities was estimated using speed-specific or activity-specific MET values from the Compendium of Physical Activities.²² MET-min per week (min/wk) were then calculated by multiplying the MET value for each activity by frequency and duration. Then, MET-min/wk for all activities was added together. For the present study, participants were classified into three categories based on the 2008 Physical Activity Guidelines for Americans:²³ inactive (0 MET-min/wk), insufficient (1-499 MET-min/wk), and recommended (≥ 500 MET-min/wk).

AHA Ideal Cardiovascular Health. Ideal CVH was determined by assessing the presence of seven positive health factors and behaviors that include: abstinence from smoking within the past year, ideal body mass index, physical activity at goal levels, consumption of a dietary pattern that promotes cardiovascular health, untreated total cholesterol (<200 mg/dL), untreated blood pressure (<120/80 mmHg), and the absence of diabetes mellitus and clinical CVD.³ Each of these ideal CVH metrics will be classified as poor (value of 0), intermediate (1) or ideal (2). Ideal CVH was calculated by summing the scores across all seven categories, with each poor metric receiving no points, each intermediate metric receiving one point, and each ideal metric receiving two points. Participants' were categorized based on their total ideal CVH score out of 14 possible points as follows: inadequate (0-4 points), average (5-9 points), and optimum (10-14 points).

Change in total ideal CVH score as a discrete variable was calculated as the difference in total ideal CVH score between the first two adjunct examinations, and divided by the number of years between them. Change in total ideal CVH score was categorized by grouping participants into categories of loss, stable, or gain, based on tertiles of change as described above for change in CRF categories.

Data Analysis

Baseline characteristics were summarized for the total population and by sex. Differences between sexes at baseline were determined by t-tests for continuous variables and chi-square tests for categorical variables. Multivariable

general linear and logistic regression models were used to evaluate the association of baseline CRF with baseline ideal CVH score and to estimate the odds of being in the average or optimum ideal CVH categories by baseline CRF categories, respectively. These cross-sectional analyses controlled for age, sex, and year of examination.

To investigate the longitudinal association between changes in CRF and changes in ideal CVH, we employed linear regression models adjusting for age, sex, and time between exam dates. Separate models that included CRF and ideal CVH as either continuous or categorical variables were used. All models were performed in the total population and stratified by sex (removing sex as covariate in model).

SAS version 9.4 was used for all statistical analyses. The threshold for statistical significance was set at the $p < 0.05$ level.

Aim 2

Aim 2 established cutpoints in order to define responsiveness for change in $\dot{V}O_{2\max}$ following standardized aerobic exercise interventions (Objective 2.1). Using this definition, assessment of the prevalence of low $\dot{V}O_{2\max}$ response across 14 large, standardized aerobic exercise interventions was completed (Objective 2.2). Furthermore, aim 2 examined whether exercise dose, intensity, and/or program duration is associated with the prevalence of low $\dot{V}O_{2\max}$ response (Objective 2.3). Subsequently, Aim 2 investigated the relationship between changes in $\dot{V}O_{2\max}$ and changes in cardiometabolic risk factors (resting SBP and fasting plasma insulin, HDL-C, and TG) utilizing these 14 aerobic

exercise interventions. This aim compared the difference of changes in cardiometabolic risk factors between $\dot{V}O_{2\max}$ response groups (Objective 2.4). Additionally, this aim explored the distribution of low responses across all traits via a total risk factor response score (Objective 2.5).

Study Design

This study employed both cross-sectional and longitudinal designs to analyze data from previously completed experimental trials. A longitudinal design was used to determine participants' change in $\dot{V}O_{2\max}$ from baseline to post aerobic exercise intervention. Two cutpoints were applied to the $\dot{V}O_{2\max}$ change scores in order to define low $\dot{V}O_{2\max}$ response in both absolute and relative terms. Subsequently, these created categories of $\dot{V}O_{2\max}$ responsiveness were used in a cross-sectional analysis in order to determine the prevalence of low $\dot{V}O_{2\max}$ response for each intervention and determine if $\dot{V}O_{2\max}$ responsiveness is related to concomitant changes in cardiometabolic risk factors. To address aim 2, data from 14 completed aerobic exercise interventions from eight of the largest exercise training studies was utilized.

Study Population

The present study examined data from 14 distinct supervised exercise interventions (n=1,724) from the following completed exercise training studies: Health, Risk Factors, Exercise Training And Genetics Family Study (HERITAGE), Dose-Response to Exercise in Women (DREW), Gene Exercise Research Study (GERS), Energy Flux, Examination of Mechanisms of Exercise-induced Weight Compensation (E- MECHANIC), Inflammation and Exercise (INFLAME), and

Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE) I and II. These interventions provide a diverse array of populations, standardized exercise programs, and baseline fitness levels. Overall, these exercise interventions ranged from doses of 4-35 kcal·kg⁻¹·week⁻¹ (KKW); intensities of 50-85% $\dot{V}O_{2max}$; and durations of 20-35 weeks. All participants from these exercise training studies received written and oral informed consent. The studies were all reviewed and approved by each institution's Institutional Review Board.

Exercise Training Study Protocols

DREW. The DREW Study was a randomized controlled dose-response exercise trial. The present study sample will include 361 previously sedentary, postmenopausal women (63% White) with a BMI of 25-40 kg/m², resting systolic blood pressure of 120-159 mmHg, and resting diastolic blood pressure ≤99 mmHg who completed one of three 24-week aerobic exercise programs. The three exercise programs expended 4 (n=155), 8 (n=104), or 12 (n=102) kcal per kg of body weight per week (KKW). All participants alternated training sessions on a cycle ergometer or treadmill with a target intensity of 50% $\dot{V}O_{2max}$. Exercise training sessions were completed three to four times per week.²⁴

GERS. The GERS sample will include 171 previously sedentary, non-diabetic, non-smoking men and women (56%) aged 50-71 years (73% White). Participants had no history of CVD, were normotensive or had medication-controlled blood pressure, and had a BMI <37 kg/m². The exercise training program consisted of 24 weeks (three sessions per week) of aerobic exercise.

Participants used various types of aerobic exercise equipment including cycle ergometers, treadmills, rowers, and elliptical, skier, and stepping machines.²⁵

Exercise training progressed to a target exercise intensity of 70% $\dot{V}O_{2\max}$.^{26, 27}

HERITAGE. The HERITAGE sample included 718 (66% White) men and women (56%) aged 17-65 years who completed a 20-week endurance exercise program. Participants were sedentary at baseline, normotensive to untreated mildly hypertensive (<160/100), and body mass index (BMI) was less than 40.0 kg/m². The exercise program consisted of aerobic exercise performed three days per week on a cycle ergometer. Training progressed to a target exercise intensity of 75% $\dot{V}O_{2\max}$.²⁸

Energy Flux. The Energy Flux Study was a randomized controlled exercise trial. The present study sample will include 65 men and women (46%) aged 21-45 years (48% White) who completed one of two 24-week aerobic exercise interventions. Participants were previously sedentary, generally healthy adults with a BMI of 25-35 kg/m². The two exercise intervention programs expended 17.5 (n=33) or 35 (n=32) KKW. Training progressed to target exercise intensity 70-75% maximal heart rate (HR) (based on most recent maximal exercise test). All exercise was performed on a treadmill 3-6 times per week.

INFLAME. The INFLAME sample will include 66 previously sedentary, generally healthy, non-smoking men and women (65%) who completed a 16-week aerobic exercise intervention. Participants (65% White) were aged 30-75 years with a BMI 18-40 kg/m², blood pressure <140/90 mmHg, and elevated plasma C-Reactive Protein concentration (≥ 2.0 mg/L but <10.0 mg/L) at baseline.

Exercise training expended 16 KKW at a target exercise intensity 60-80% $\dot{V}O_{2max}$. Exercise was performed on either a treadmill or cycle ergometer 3-5 times per week.²⁹

E-MECHANIC. E-MECHANIC was a six-month randomized controlled exercise trial. The sample to be used for the present study includes 117 men and women (72%) who completed one of two aerobic exercise interventions. Participants (68% White) were non-smoking, generally healthy, previously sedentary adults (aged 18-65 years) with a BMI of 25-45 kg/m². The two exercise groups expended 8 (n=60) or 20 (n=57) KKW for 24 weeks. All exercise was performed on a treadmill at a target intensity of 65-85% $\dot{V}O_{2max}$. Exercise sessions were completed 3-5 times per week.³⁰

STRIDE. The STRIDE I and II studies were randomized controlled exercise trials lasting for eight months. The present study sample includes 227 (83% White) non-smoking men and women (50%) who completed one of four exercise training interventions. Participants were free of diabetes and coronary artery disease, aged 40-65 years with a BMI 25-35 kg/m², resting blood pressure <160/90 mmHg, and mild-to-moderate dyslipidemia [low-density lipoprotein cholesterol (LDL-C) 130-190 mg/dL and/or HDL-C 40mg/dL (men) or 45 mg/dL (women)]. Combining STRIDE I and II, participants completed one of four exercise interventions: mild (14 KKW; 40-55% $\dot{V}O_{2peak}$; n=36), moderate (14 KKW; 65-80% $\dot{V}O_{2peak}$; n=90), high (23 KKW; 65-80% $\dot{V}O_{2peak}$; n=57), or moderate plus resistance training (three days per week, three sets per day, and

8-12 repetitions per set; n=44). Aerobic exercise was performed three times per week on treadmills, elliptical machines, or cycle ergometers.^{31, 32}

Study-Specific Measurements

DREW. Full details of the DREW study design and methods are available elsewhere.²⁴ The DREW Study participants completed laboratory and self-report measures at baseline and six months. Measures included: $\dot{V}O_{2\max}$, resting BP, anthropometry, dietary habits, PA history, medication use, menstrual history, personal and family medical history, and fasting cholesterol, TG, and glucose. $\dot{V}O_{2\max}$ was assessed via two maximal cycle ergometer tests on separate days at baseline and follow-up. Participants practiced on the cycle ergometer during the initial baseline medical assessment. Prior to exercise testing, resting electrocardiography (ECG), heart rate (HR), and BP were measured. Participants exercised at 30 Watts (W) for 2 min, 50 W for 4 min, followed by increases of 20 W every 2 min until exhaustion. Throughout the test, BP, HR, ECG, $\dot{V}O_2$, carbon dioxide (CO_2) production, ventilation and respiratory exchange ratio (RER) were measured. Respiratory gases were measured using a ParvoMedics True Max 2400 metabolic measurement cart (Sandy, UT). Two fitness tests were performed on separate days at baseline and follow-up. The average $\dot{V}O_{2\max}$ from these two tests was used as $\dot{V}O_{2\max}$.

Following a 30-min recumbent rest period, at least four BP measurements were taken using an automated BP unit (Colin STBP-780). Each BP measurement was separated by two min.

At baseline and follow-up, blood samples were obtained via an antecubital vein following a 10-12 hr fast. Fasting blood glucose concentration and blood lipid profiles were determined with a Dimension RXL analyzer (Oxford, CT). Additionally, plasma insulin was measured by electrochemiluminescence.

GERS. Full details of the GERS study design and methods are available elsewhere.^{26, 27} Study measurements included medical history, fasting blood samples (genotyping and plasma lipids), glucose tolerance testing, physical and cardiovascular examination by a physician, and maximal exercise testing at baseline and post-training. $\dot{V}O_{2\max}$ was assessed via Bruce maximal treadmill exercise testing.³³ HR, BP, and ECG results were recorded prior to the start of the test, at the end of each exercise stage, and after completion of the test. $\dot{V}O_2$ was measured continuously and directly throughout the test using a customized metabolic system (Marquette Respiratory Mass Spectrometer, Rayfield Mixing Chamber, VMM Ventilatory Turbine).

Participants were fasted and sat quietly in the laboratory for 15 min prior to resting BP measurements were obtained. BP was measured while the participants were seated with their arm at heart level. Two measurement values had to agree within ± 5 mmHg. Averages from two days of BP measures were used to determine resting BP.

Blood samples were obtained in the morning following an overnight fast. For plasma lipid levels, blood samples were taken on two separate days and averaged. At least three days before exercise training began, blood samples were drawn after the completion of the 6-wk dietary stabilization period. Post-

training samples were obtained 24-36 hr after the participant's final exercise training session. Plasma insulin levels were determined via radioimmunoassay (Linco Research, St. Charles, MO). Plasma HDL-C levels were measured after precipitation with dextran sulfate on a CDC-certified Hitachi 717 analyzer.

HERITAGE. Full details of the HERITAGE study design and methods are reported elsewhere.²⁸ Participant measures included: blood samples (plasma lipids, glucose, insulin, sex steroids, glucocorticoids), body fat and fat distribution, dietary and activity habits (questionnaires), several genetic analyses, and two maximal exercise tests at baseline and follow-up. These two tests were conducted at approximately the same time of day with at least 48 hrs between the two tests. All maximal exercise tests were performed on a cycle ergometer and included the following measures: ventilatory rate (\dot{V}_E), $\dot{V}O_2$, volume of carbon dioxide expired ($\dot{V}CO_2$), RER, BP, HR, cardiac output, stroke volume, and blood variables (glucose, free-fatty acids, lactate, and total proteins).

Respiratory gases were measured by using a SensorMedics 2900 metabolic cart. The average $\dot{V}O_{2max}$ from the two tests was calculated and recorded as $\dot{V}O_{2max}$ for each subject given that both values were within 5% of each other. If $\dot{V}O_{2max}$ from the two tests differed by more than 5%, the higher $\dot{V}O_{2max}$ value was used.

Following a 5-min rest period, resting BP was measured using an automated blood pressure unit (Colin STBP-780; San Antonio, TX). At 2-min intervals, four readings were taken. Resting BP was recorded as the mean of three or more reliable measurements.

Blood samples were obtained from venipuncture of an antecubital vein into vacutainer tubes containing EDTA. Blood draws were performed in the morning following a 12-hr fast. Blood samples were collected twice at baseline on separate days. Post-training blood samples were taken at 24 and 72 hr after the final training session. Samples were obtained early in the follicular phase of the menstrual cycle for eumenorrheic women. Total cholesterol and TG levels were determined in plasma and lipoproteins by enzymatic methods (Technicon RA-500 Analyzer; Bayer Corporation Inc., Tarrytown, NY). HDL-C fractions were obtained after precipitation of LDL in the infranant via the heparin manganese chloride method. Fasting plasma insulin samples were obtained at baseline as well as one and three days after the final exercise bout. Plasma insulin (i.e., immunoreactive insulin) was measured by radioimmunoassay following polyethylene glycol separation.

Energy Flux. Full details of the Energy Flux Study design and methods are in submission. Measurements of body composition, energy expenditure, resting metabolic rate, peak oxygen consumption ($\dot{V}O_{2peak}$), dietary intake (four day diet recall), blood chemistry (glucose, leptin, grehlin, C-reactive protein, apolipoprotein B, β -hydroxybutyrate, a lipid panel), and several questionnaires regarding health behavior, current mood status, and overall health were completed at baseline, three and six months. $\dot{V}O_{2peak}$ was assessed on a treadmill using a modified Bruce protocol with ECG. This exercise test consisted of two-minute stages in which the participants worked to volitional fatigue, as previously described.³⁴ BP, HR, and rating of perceived exertion (RPE) were

recorded during the last 30 seconds (s) of each stage. Expired gases were collected continuously via a stationary metabolic system (True One 2400, ParvoMedics, Sandy, UT) to determine $\dot{V}O_{2peak}$. Participants in both exercise groups performed a second fitness test at the end of the four-week run-in period to adjust exercise intensity due to potential acute training adaptations.

Resting BP was measured using a sphygmomanometer and stethoscope while the participant was sitting quietly. At least two measurements were taken to be within 10 mmHg for systolic BP and within 5 mmHg for diastolic BP. The average of the measurements was recorded as resting BP.

Following a 12-hr fast and 24-hr abstention from physical activity, blood samples were obtained at baseline, 3-months, and 6-months (post-intervention). Blood samples were obtained from an antecubital vein into tubes containing EDTA. Samples were stored at -80°C and sent in entirety to LabCorp (Columbia, SC) for fasting HDL-C, TG, and insulin analysis upon completion of the study.

INFLAME. Full details of the INFLAME design and methods can be obtained elsewhere.²⁹ Study measurements were completed at baseline and post-training and included the following: anthropometrics, blood chemistry (C-reactive protein, lipids, fasting glucose, and insulin), BP, CRF, and energy intake. Fitness testing was performed on a cycle ergometer with ECG. Participants cycled at 30 W for 2 min, 50 W for 4 min, and subsequent increases of 20 W every 2 min until participants could no longer maintain a pedal cadence of 50 rpm. Throughout the test, HR, RPE, $\dot{V}O_2$, CO_2 production, ventilation, and RER

were recorded. Respiratory gases were measured using a ParvoMedics' TrueOne 2400 (Sandy, UT) Metabolic Measurement Cart.³⁵

At least four BP measurements were performed after a 30-min recumbent rest period using an automated blood pressure unit (Colin STBP-780). Each measurement was separated by 2 min.

Throughout the trial, blood samples were taken at three separate visits: 3 ml at the orientation session, 20 ml at baseline (approximately two weeks later), and 20 ml at the 4-month follow-up assessment. Participants were fasted for 10-12 hr for each of the blood samples. Additionally, participants refrained from consuming alcohol or exercising for 24 hr and acutely refrained from using aspirin or anti-inflammatory medications for 48 hr prior to blood samples being obtained. Plasma insulin was measured by electrochemiluminescence. Fasting blood glucose concentration and blood lipid profiles were measured with a Dimension RXL analyzer.

E-MECHANIC. Details of the E-MECHANIC study design and methods are available elsewhere.³⁰ Primary assessments for this study occurred at baseline and post-training (24 weeks), and also utilized a truncated assessment period at week 4 to identify potential short-term changes in outcome variables. Participant assessments included anthropometrics, body composition, energy metabolism, physical activity (including $\dot{V}O_{2max}$), and blood chemistry. $\dot{V}O_{2peak}$ was determined by a graded treadmill exercise test. Treadmill speed began at 2.4 mph on a level grade for two min. Treadmill speed and/or grade increased every two min until volitional fatigue was reached. Throughout the intervention,

caloric expenditure rate was measured during exercise training with a metabolic cart. At least two resting BP measurements were taken after the participant rested in a seated position for at least five min.

STRIDE. For the STRIDE (i.e., STRIDE I) and STRIDE AT/RT (i.e., STRIDE II) studies, full details of study design and methods are available elsewhere.^{31, 32, 36} Study measurements included anthropometrics, BP, blood chemistry (carbohydrate and lipid metabolism), food intake, Metabolic Syndrome z score, and cardiorespiratory fitness at baseline and post-training.³¹ Additionally in STRIDE II, overall strength was measured.³² To assess $\dot{V}O_{2peak}$, maximal cardiopulmonary exercise tests with ECG and expired gas analysis were performed on a treadmill. Expired gases were measured using a ParvoMedics' TrueMax 2400 Metabolic Cart (Sandy, UT). The protocol consisted of 2-min stages, increasing the work rate by approximately 1 MET per stage. The $\dot{V}O_2$ for the last 40 s of each state were averaged to determine $\dot{V}O_{2peak}$.

For STRIDE I, resting BP was measured in the standing position just prior to maximal exercise testing. For STRIDE II, resting BP was taken every 20 min during the last hr of the 3-hr intravenous glucose tolerance test (GTT). Values were averaged to obtain resting BP.

Fasted blood samples were taken at baseline and post-intervention approximately 30-min prior to the start of the GTT. In regards to post-intervention, blood samples were obtained 16-24 hr after the final exercise training session. Blood samples were taken into EDTA tubes from an intravenous catheter in the antecubital area. In order to control for inter-technician and inter-

assay variability, pre- and post-intervention plasma samples from the same subject were analyzed together. Fasting insulin was measured by immunoassay (Access Immunoassay System, Beckman Coulter, Fullerton, CA). Fasting HDL-C and TG concentrations were estimated with NMR spectroscopy (LipoScience, Raleigh, NC).

Data Analysis

In order to quantify low $\dot{V}O_{2\max}$ responsiveness, we applied the findings of Skinner et al.'s report regarding the reproducibility of $\dot{V}O_{2\max}$ measured from maximal exercise testing in HERITAGE to the additional aerobic exercise interventions.³⁷ Based on technical error (TE) and coefficient of variation values derived from this study, low $\dot{V}O_{2\max}$ response was defined in both absolute (gain <120 ml/min from baseline value) and relative (gain <5% of study-specific baseline average $\dot{V}O_{2\max}$) terms. Subsequently, the prevalence of low $\dot{V}O_{2\max}$ response across interventions was calculated based on both the absolute and relative definitions. We used within-study group comparisons to compare the relative low $\dot{V}O_{2\max}$ responsiveness within studies that employed multiple exercise interventions.

Based on previous literature from HERITAGE,³⁷⁻⁴² low response for each cardiometabolic trait following exercise training was defined as any change value beyond 1xTE in a direction indicating a worsening of the risk factor was considered a low response. Baseline characteristics were summarized for the total population and by study. Prevalence of low response for each trait was assessed on the basis of the number of participants who exceeded the 1xTE

calculations. For each of the cardiometabolic risk factors, a logistic regression was performed to compare the distribution of low response between $\dot{V}O_{2\max}$ response groups.

A total response score for all of the cardiometabolic risk factors was calculated for each participant. Each risk factor classified as a low response received no points, while each risk factor classified as a response received one point. Thus, a participant that did not display any low responses would receive four total points for their cardiometabolic risk factor score. A X^2 test was performed to compare the distribution of the total response score between $\dot{V}O_{2\max}$ (relative) response groups. SAS version 9.4 was used for all statistical analyses. The threshold for statistical significance was set at the $p = 0.05$ level.

CHAPTER 3

LITERATURE REVIEW

Cardiorespiratory fitness

CRF is defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen to the body in order to perform physical work. Since CRF integrates numerous systems in the body, CRF quantifies the functional capacity of an individual and reflects total body health. CRF can be measured directly via maximal exercise tests and is expressed as $\dot{V}O_{2max}$. Although less precise, estimated CRF can be easily derived from the peak work rate achieved on a treadmill or cycle ergometer. Estimated CRF is commonly expressed in terms of metabolic equivalents (METs; a multiple of the resting metabolic rate approximating $3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Cardiorespiratory fitness and mortality risk

Whether estimated or measured directly, mounting evidence has developed over the past 30 years establishing a strong inverse relationship between CRF and risk for CVD and all-cause mortality.^{17, 43, 44} Additionally, low levels of CRF are associated with higher mortality rates attributable to several cancers, especially colon and breast cancers.⁴⁵ Moreover, mortality risk is notably reduced as CRF improves.⁴⁶ In a recent scientific statement from the AHA concerning the importance of assessing CRF as a clinical vital sign, Ross and colleagues⁴⁷ highlighted several critical references that express CRF in the

terms of survival benefit per MET. Collectively, these studies showed that each 1-MET increment in CRF, which is a small, relatively attainable increment in fitness, was associated with a 10-25% improvement in survival.⁴⁷ Furthermore, mortality risk reduction has even been shown to decrease by as much as 30% in low fit individuals (peak MET level <5) with CVD who improved exercise capacity following cardiac rehabilitation participation.⁴⁸

Recently, Naci and Ioannidis published a network meta-analysis to compare the effectiveness of exercise and pharmaceutical drug intervention on mortality risk.⁴⁹ This study included 16 meta-analyses (12 drug and four exercise) along with three additional recent exercise trials, which collectively totaled 305 randomized controlled trials (n=339,274). This analysis examined the benefits of exercise on the secondary prevention of coronary heart disease, treatment of heart failure, diabetes prevention, and stroke rehabilitation. This study did not find a statistical difference between exercise and pharmaceutical interventions in terms of mortality benefits for secondary prevention of coronary heart disease and diabetes. The results also showed that exercise and physical activity interventions were actually more effective than pharmaceutical interventions for the secondary prevention of stroke mortality. The authors noted that evidence from randomized controlled trials regarding mortality benefits from exercise intervention is scarce, especially when compared to the pharmaceutical intervention evidence (only 57 out of 305 trials were exercise interventions). Despite this limitation in the evidence base, Naci and Ioannidis's study suggests

that exercise and drug interventions are potentially similar in effectiveness for mortality benefits.⁴⁹

Cardiorespiratory fitness and cardiovascular disease risk

Several recent studies have shown the prominent role that CRF plays as a predictor of adverse CVH outcomes (e.g., acute myocardial infarction, ischemic heart disease, and CVD mortality). Compared to traditional risk factors, such as hypertension (HTN), insulin resistance, lipid abnormalities, smoking, and obesity, low CRF is the strongest predictor of risk for adverse CVH outcomes, including mortality.⁵⁰⁻⁵⁸ Remarkably, CRF level is not solely a critical risk factor for CVD; CRF also plays an influential role as a moderator for traditional CVD risk factors.

Hypertension

Chronic HTN is a major risk factor for CVD. Among individuals who develop adverse CVH outcomes, HTN is the most common risk factor. As stated by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the direct relationship between CVD risk and blood pressure (BP) begins at 115/75 mmHg.⁵⁹ For each increment of 20/10 mmHg, CVD risk doubles.⁶⁰

In 1984, Blair and colleagues were the first to investigate the relationship between measured CRF and HTN incident.⁶¹ Participants were normotensive, predominantly white, well-educated men and women (n=6,039) from the Aerobics Center Longitudinal Study (ACLS). Participant follow-up ranged from one to 12 years. Blair *et al.* found that low fit individuals had a 1.5 times increased risk for developing HTN compared to high fit individuals, even after controlling for age,

sex, body mass index, baseline BP, and follow-up interval. For low fit individuals that were also in the highest BP category at baseline, risk for developing HTN increased tenfold.⁶¹ These findings were confirmed by Sawada *et al.*⁶² in 3,305 normotensive Japanese men that were followed for five years. After adjusting for age, body fat, baseline BP, and additional confounding variables, relative risk for the development of HTN was 1.9 times greater for the least fit group compared to the group with the highest fitness level.⁶² In 2003, Carnethon *et al.* looked at the relationship between CRF in young adulthood and the development of CVD risk factors in 2,478 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study. The authors reported that each one-minute decrease in maximal treadmill time performance was associated with a 19% higher 15-year risk of incident HTN among men and women after adjustment for age, sex, weight gain, and other confounding variables.⁶³ In addition, a subsequent study from the ACLS examined the association between CRF and incident HTN exclusively in women who were normotensive at baseline. Results showed that for each 1-MET increment in maximal exercise treadmill test performance, there were 19% lower odds for developing HTN.⁶⁴

Lifestyle interventions, such as increased physical activity and weight loss, contribute significantly to successful BP control. These positive lifestyle modifications provide beneficial changes in BP with minimal side effects.⁶⁵ Several meta-analyses have reviewed numerous well-controlled aerobic exercise studies and have consistently documented significant reductions in resting BP following intervention.⁶⁶⁻⁸² Thus, leading organizations around the world

recommend approaches that include regular physical activity to prevent and treat HTN.^{59, 83-86}

In 2013, Cornelissen and Smart published the largest meta-analysis to date on randomized controlled trials investigating the effects of exercise training on resting blood pressure (n=5,223; 3,401 exercisers and 1,822 sedentary controls).⁸⁰ This study included exercise interventions of endurance (105 groups), dynamic resistance (29 groups), combined endurance and resistance training (14 groups), and isometric resistance training (5 groups) in adults who ranged from normotensive to hypertensive. For the purpose of this literature review, discussion focuses on endurance exercise training. Overall, training duration ranged from four to 52 weeks and included one to seven exercise sessions per week (majority of sessions lasted 30-60 minutes). Exercise intensity ranged from 35-95% $\dot{V}O_{2peak}$. Endurance exercise training-mediated decreases in BP averaged 3.5 mmHg for systolic BP and 2.5 mmHg for diastolic BP. Additionally, the largest reductions in BP following endurance training were significantly greater in hypertensive individuals compared to prehypertensive and normotensive individuals. These results are consistent with previous systematic reviews stating that structured aerobic exercise interventions of moderate intensity and adequate volume result in an independent reduction in resting BP of approximately 4-10 mmHg in systolic and 3-8 mmHg diastolic BP regardless of age or sex for individuals with stage 1 HTN.^{65, 85, 87, 88} Based in part upon this scientific evidence, Pescatello and colleagues published an exercise prescription update regarding HTN.⁸⁹ This updated exercise prescription includes the

following to elicit the greatest BP benefit for adults with HTN: ≥ 30 minutes per day of moderate intensity aerobic exercise on most days of the week and dynamic resistance exercise 2-3 days per week, totaling ≥ 150 minutes of exercise per week.

Insulin resistance

Insulin resistance develops when the body produces insulin but does not use insulin efficiently to uptake glucose into cells for energy usage and storage, causing a buildup of glucose in the blood. This hyperglycemic state triggers the pancreas to increase β -cell production of insulin to try to counteract the high levels of blood glucose. Eventually, the β -cells can no longer meet the demands for insulin production caused by hyperglycemia, exacerbating the levels of glucose in the blood. Insulin resistance can lead to the development of Type 2 diabetes mellitus (T2D) and CVD. As stated by the AHA, an individual with T2D is at approximately two to four times greater risk for dying from CVD compared to a non-diabetic individual.^{2, 90}

Several large observational cohort studies, including the Harvard Alumni Study⁹¹, US male physicians⁹², and the Nurses' Health Study^{93, 94}, have established physical activity participation as a highly effective way to avert or delay T2D onset, and can reduce adverse CVH outcome and mortality risk amongst those with T2D. In addition to general physical activity participation, there is a well-documented, inverse, curvilinear association between CRF and risk of prediabetes, T2D, and metabolic syndrome.^{93, 95-99} Individuals with moderate to high levels of CRF only have small differences in T2D risk rates

between each CRF level. Conversely, those with low CRF that gain small increments in CRF are associated with large decreases in risk for developing T2D, highlighting the importance of physical activity and exercise interventions targeting individuals who are the least fit and stand the most to gain from improved CRF.⁴⁷

In the human body, skeletal muscle is the largest consumer of glucose. Not only does insulin stimulate uptake of glucose into muscle cells, but these cells also have glucose transporter proteins, GLUT-4 specifically, that instigate glucose uptake. Exercise increases glucose uptake into working muscle cells via the GLUT-4 transporter in an insulin-independent manner.¹⁰⁰ A strong evidence base exists with numerous exercise training studies supporting the idea that both aerobic and anaerobic exercise training can improve both glucose uptake and insulin sensitivity, making exercise a remarkable modulator for T2D and CVD risk.^{101, 102}

The seminal study by the Diabetes Prevention Program study provided strong evidence that lifestyle modifications including diet and exercise were *more effective* than pharmaceutical treatment using metformin in reducing the incidence of T2D.¹⁰³ Participants (n=3,234) were nondiabetic and had elevated fasting and post-load plasma glucose concentrations. Participants were randomized to one of three groups: placebo, metformin (850 mg twice daily), or a lifestyle modification group. Participants in the lifestyle intervention group were encouraged to achieve goals of 7% weight loss and ≥ 150 minutes per week of physical activity. After an average follow-up time of 2.8 years, the lifestyle

intervention reduced T2D incidence by 58%, which was significantly greater than the 31% reduction in the metformin group. This study stated that in order to prevent a single case of T2D during a three-year period, 6.9 individuals would have to participate in the lifestyle intervention, while 13.9 individuals would have to receive metformin.

In 2014, Conn and colleagues were the first to publish a comprehensive meta-analysis regarding the effects of supervised exercise training on insulin sensitivity in healthy adults.¹⁰⁴ This analysis included both published and unpublished exercise intervention studies that measured insulin sensitivity, and included 78 study reports and a total of 2,509 men and women. Unfortunately, only 68 of the reports provided adequate details of the exercise intervention. Of those reported, the median of the average exercise session time during supervised training was 51 minutes; the median of average session frequency was three per week; and the median of mean total number of exercise sessions was 51. Overall, this review documented moderate improvements in insulin sensitivity in healthy adults following supervised exercise interventions (mean effect size 0.38 and 0.43).

Recently, Bird and Hawley reviewed the literature regarding the effects of physical activity and exercise on insulin sensitivity to provide an update on the latest research published between 2013 and 2016.¹⁰⁵ In addition to furthering the support of physical activity's beneficial association with insulin sensitivity, the authors summarized the following new findings: aerobic exercise may increase insulin sensitivity without a detectable increase in $\dot{V}O_{2\max}$, a dose effect is

emerging that shows increases in both exercise volume and intensity modulate insulin sensitivity, aerobic exercise combined with resistance exercise may be the most effective approach compared to either exercise mode alone, and exercise induced benefits in insulin sensitivity may be augmented by appropriate dietary changes.

Dyslipidemia

Another major risk factor for CVD is dyslipidemia, a condition in which plasma cholesterol, TG, or both are elevated. Dyslipidemia can include both low levels of HDL-C; (HDL particles remove cholesterol from arteries) and high levels of LDL-C (LDL particles increase fatty deposits in arteries), which leads to increased risk of plaque buildup and blockages. Prevalence of lipid abnormalities in the United States estimated from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) are as follows: 53% of U.S. adults have lipid abnormalities; 27% have high LDL-C; 23% have low HDL-C; and 30% have high TG. In a previous epidemiological study from 2000, low levels of HDL-C and elevated total cholesterol to HDL-C ratios were independently associated with risk for coronary artery disease (CAD). For every 1 mg/dL increase in HDL-C, there was a 2% decreased risk for CAD in men and a 3% reduction in risk for women.¹⁰⁶

In 2015, Sarzynski *et al.*¹⁰⁷ examined the associations of baseline CRF and changes in CRF on incident dyslipidemias in participants from the CARDIA study (n=4,898). Over a 25-yr follow-up period, a significant inverse relationship was found between the 25-yr incidence rate for each dyslipidemic trait (low HDL-

C, high TG, and high LDL-C) and baseline CRF. For example, the 25-yr incident rate for high TG was 42% lower in the highest CRF quartile at baseline compared to the lowest CRF quartile. For each of these dyslipidemic traits, those in the highest sex-specific CRF quartile at baseline had significantly lower incidence rates than the other three CRF quartiles. For each additional stage completed during maximal fitness testing (two min per stage), risk for incident low HDL-C, high TG, and high LDL-C was decreased by 9%, 16%, and 14%, respectively. When evaluating the influence of sex and race, the association of baseline CRF with 25-yr incidence of high TG appeared to be limited to white participants only. There were no significant associations found in black participants. Longitudinal results from adjusted regression models were not significant for the prediction of 5-yr incidence of dyslipidemias based on 20-yr change in CRF. On the other hand, baseline CRF did significantly predict 5-yr incidence of high TG.¹⁰⁷ The results from this study support the notion that achieving higher levels of CRF are related to decreased risk for incidence of dyslipidemias, particularly high TG.

A recent report looked at the impact of both baseline CRF and changes in CRF on the risk for developing atherogenic dyslipidemia in men and women from the ACLS.¹⁰⁸ Atherogenic dyslipidemia was defined by the following: low HDL-C (<40 mg/dL), high LDL-C (≥ 160 mg/dL), and high TG (≥ 200 mg/dL). A total of 9,651 participants were followed over an average of 8.9 years. During follow-up, 193 participants developed atherogenic dyslipidemia. Participants with high levels of CRF at baseline had 43% lower odds of developing atherogenic dyslipidemia compared to low fit individuals. However, once baseline HDL-C,

LDL-C, and TG were accounted for in the analysis, this association became nonsignificant. When looking at changes in CRF over time, participants who maintained their fitness level had 43% lower odds of developing atherogenic dyslipidemia compared to those who had a reduction in CRF level. This relationship remained statistically significant after additional adjustment for baseline lipid metrics.¹⁰⁸ Therefore, this study demonstrated a protective effect of CRF against the risk for developing atherogenic dyslipidemia.

The majority of epidemiological and clinical evidence supports the following concept: when adequate intensity, duration, and volume of aerobic exercise are performed by both healthy individuals and those with dyslipidemia, there are favorable and independent alterations in blood lipids and lipoproteins.^{88, 109-111} Mounting evidence exists suggesting that the magnitude of changes in HDL-C is related more to the *volume* of exercise rather than the intensity.^{109, 110, 112} To achieve significant changes in HDL-C, volume of exercise needed is estimated to be 1,000 to 1,500 kcal/week.^{113,88}

When looking at the components of dyslipidemia, the evidence describing increases in HDL-C with exercise is more consistent in comparison to the evidence describing reductions in total cholesterol, LDL-C, and TG concentrations.^{111, 112, 114} LDL-C is largely unaffected by regular exercise when body weight and diet remain unchanged.¹¹⁴⁻¹¹⁶ When exercise is combined with alterations in diet in patients with dyslipidemia, LDL-C reductions can be greater compared to reductions achieved by diet or exercise alone.¹¹⁷ Furthermore,

exercise training has been shown to attenuate reductions in HDL-C that typically result from low-fat diets.¹¹⁷⁻¹²⁰

Kodama and colleagues performed a meta-analysis investigating the effects of aerobic exercise training studies on HDL-C.¹²¹ Twenty-five aerobic training randomized controlled trials were included for review. Average intervention duration was 27 weeks with a mean frequency of 3.7 sessions per week, mean session time of 40.5 minutes, mean estimated energy expenditure was 1,019 kcal/week, and mean absolute and relative intensity was 64.8% $\dot{V}O_{2max}$ and 5.3 METs, respectively. Overall, the exercise interventions produced a modest, yet highly significant beneficial change in HDL-C of 2.53 mg/dL. This analysis estimated a minimal exercise volume threshold of 900 kcal/week or 120 minutes of total exercise per week to induce a significant elevation in HDL-C. In addition, each 10-minute increase in exercise duration corresponded to approximately a 1.4 mg/dL elevation in HDL-C. Finally, exercise training was found to be more effective in participants with lower body mass index or higher baseline HDL-C levels.

Overweight and obesity

According to the World Health Organization (WHO), overweight (OW) and obesity (OB) are classified by the following: OW is a body mass index (BMI) between 25.0-29.9 kg/m² and OB is a BMI greater than or equal to 30 kg/m². Based upon NHANES data from 2009-2012, 69% of U.S. adults are OW and 35% are considered OB.¹²² As documented by numerous reports, there is a strong association between OW/OB and increased prevalence of CVD, making

OW and OB well-established CVD risk factors.¹²²⁻¹²⁸ In addition, excess risk results from OW and OB coexisting with several other major CVD risk factors, like HTN, atherosclerosis, metabolic syndrome, dyslipidemia, T2D, and obstructive sleep apnea.¹²⁹ Increased adiposity, especially visceral adiposity, has also been shown to independently provoke alterations in cardiac structure and function, further compounding the effects of OB on CVD risk.^{129, 130}

Both central and peripheral hemodynamics are altered by weight gain and OB that predispose individuals to ventricular dysfunction and heart failure, including increased central and total blood volume, decreased systemic vascular resistance, and increased left ventricular (LV) stroke volume and filling pressures, cardiac output, and pulmonary artery pressures.¹³⁰⁻¹³³ OB increases the likelihood of having LV remodeling, left atrial enlargement, increased right ventricular mass, and greater end-diastolic volume.¹³⁴⁻¹³⁷ Moreover, OB is associated with LV diastolic dysfunction, subclinical LV systolic dysfunction, and reduced right ventricular ejection fraction.^{132, 138-141}

Although a strong association between excess adiposity and CVD risk exists, the evidence base demonstrating a phenomenon termed the “obesity paradox” has grown. Recent evidence from Lavie and colleagues has shown a better prognosis in patients with CVD who are OW and mildly OB compared to patients with CVD who are leaner. Patients with CVD who are underweight usually display the worst outcomes.^{131, 132} Currently, the mechanisms by which this phenomenon relates to CVD outcomes are poorly understood.¹²⁹ Although this topic is beyond the scope of this review, this growing area of research

suggests that muscle mass, strength, and CRF are major prognostic determinants in OB patients with CVD (specifically coronary artery disease and heart failure) and is important to note.¹⁴²⁻¹⁴⁵

A complex interaction exists between adiposity and CRF in regards to CVD risk and mortality, referred to as the “fit and fat” phenomenon, where high levels of CRF largely negate the adverse health effects of body fatness and additional CVD risk factors like OW/OB, T2D, and HTN.¹⁴⁶⁻¹⁵⁵ Two landmark fitness-fatness studies arose from the ACLS in 1999.^{154, 155} Both of these studies analyzed data from over 21,000 men with approximately 8-10 years of follow-up from the ACLS and found that low CRF was strongly, independently, and inversely associated with CVD and all-cause mortality, regardless of body fatness. These pivotal studies concluded that OB did not appear to increase mortality risk in fit men, and that low CRF is as important as T2D, HTN, high cholesterol, and smoking as a predictor of CVD and all-cause mortality in OW and OB men. Since then, these findings have remained consistent amongst additional ACLS reports in both men and women.¹⁵⁶ For example, in 14,345 men from the ACLS, Lee and colleagues found that each 1-MET increase in CRF between two maximal exercise tests that were on average 6.3 years apart was associated with a 15% reduction in all-cause mortality and a 19% reduction in CVD mortality (results were after adjustment for potential confounders and changes in CRF).¹⁵⁷ Change in BMI was not associated with CVD or all-cause mortality after adjustment for potential confounders and CRF change.

Additionally, men who lost fitness had higher risks of all-cause and CVD mortality regardless of change in BMI.

There are several factors that appear to play a role in the alteration of CVD risk due to increases in exercise and CRF in OW/OB patients, such as body composition, insulin resistance, endothelial dysfunction, oxidative stress, platelet reactivity, and inflammation.¹²⁹ As visceral adiposity is a strong predictor of CVD,¹⁵⁸ one example of CRF-mediated changes in CVD risk is the ability of exercise training to influence the distribution of body fat.^{36, 159-162} In 2013, Vissers *et al.* conducted a meta-analysis of 15 exercise training studies without hypocaloric diet on the effects of exercise on visceral adipose tissue (VAT) in OW adults.¹⁶² This study analyzed data from 9 controlled and 6 uncontrolled exercise trials (n=852), including aerobic, strength, or combined aerobic and strength training interventions, that had measures of VAT from computed tomography (CT) scan or magnetic resonance imaging (MRI). Overall, this meta-analysis found that aerobic training of moderate or high intensity had the greatest effect for reducing VAT in men and women compared to low intensity aerobic or strength training. This study found that after just 12 weeks of intervention, aerobic exercise training could beneficially reduce VAT (as measured by CT analysis) by more than 30 cm² in women and 40 cm² in men. Thus, this study concluded that decreases in VAT can be achieved via moderate and high intensity aerobic exercise without hypocaloric diet in OW/OB individuals, which beneficially effects CVD risk.¹⁶²

CHAPTER 4

THE ASSOCIATION OF CARDIORESPIRATORY FITNESS AND IDEAL CARDIOVASCULAR HEALTH IN THE AEROBICS CENTER LONGITUDINAL STUDY

INTRODUCTION

In 2010, the American Heart Association (AHA) established a new construct as part of the 2020 Impact Goals called ideal cardiovascular health (CVH), which is characterized by seven metrics known as Life's Simple 7 (LS7).³ The LS7 concept emphasizes seven positive health factors [blood cholesterol, blood pressure (BP), and fasting plasma glucose] and behaviors [diet quality, physical activity (PA), smoking, and body mass index (BMI)]. Each of the seven components is classified into ideal, intermediate, or poor categories and an ideal CVH score is created. A previous study from the Aerobics Center Longitudinal Study (ACLS) showed that ideal CVH was associated with risk of cardiovascular disease (CVD) mortality as demonstrated by an inverse, graded CVD mortality risk in relation to the number of ideal metrics met.¹⁶³ In addition, several cross-sectional and prospective cohort studies have found that increasing numbers of ideal CVH metrics are associated with decreased prevalence and incidence of CVD outcomes.⁴⁻¹⁶

Cardiorespiratory fitness (CRF) is well established as having a strong association with mortality and numerous CVD risk factors.¹ Despite the strong associations between CRF and each individual component of LS7, few studies have examined the independent association of CRF and ideal CVH score. Recently, Ruiz *et al.* found that CRF was positively associated with ideal CVH score in European adolescents (N=510) and identified a theoretical CRF threshold associated with a more favorable CVH profile.¹⁶⁴ However, to our knowledge no study has examined the association between CRF and ideal CVH in adults neither cross-sectionally nor longitudinally. Therefore, the purposes of our study were 1) to evaluate if CRF is associated with ideal CVH and 2) to examine the relationship between changes in CRF and changes in ideal CVH score over time in the ACLS cohort.

METHODS

Study Population

The ACLS is a prospective observational study of participants who were self-, employer-, or physician-referred for an extensive medical examination at the Cooper Clinic in Dallas, Texas. The study investigated the health outcomes associated with PA and CRF.¹⁷ All participants received written and oral informed consent and the ACLS study has been reviewed and approved annually by the Cooper Institute's Institutional Review Board. The present study included individuals with complete data on CRF and all of the AHA's LS7 health behaviors and factors between the years of 1987-1999. Participants were excluded if they had any form of CVD or cancer, or if they had abnormal findings on

electrocardiography at baseline. The final analysis included 11,590 participants who were predominately white, well-educated, and upper middle class.¹⁷

Clinical Examinations

Participants completed at least one medical examination by a physician after a 12-hour overnight fast. The medical examination was a complete preventive medical evaluation including physical examination, personal and family health history, questionnaires (demographics and health habits), anthropometry, resting electrocardiography, blood chemistry analyses, BP, and a maximal exercise treadmill test. Health history questionnaires included: personal history of myocardial infarction, stroke, hypertension, diabetes, and cancer; parental history of CVD; smoking status, alcohol intake, and PA. Participants also completed a 3-day diet recall. Time between examinations ranged from 12 months to 11 years. Details of the examinations have been described elsewhere.¹⁷

Measurements. Anthropometric measures were taken and BMI was calculated as weight in kilograms divided by height in meters squared and classified as follows: normal (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), or obese (≥ 30.0 kg/m²). Resting BP was taken following AHA protocol.¹⁷ To ensure accuracy, two measures were taken and if the readings differed by more than 5 mmHg, then a third measure was taken and all the measures were averaged. Concentrations of total cholesterol and fasting plasma glucose were measured by automated techniques that followed the standards of the Centers for Disease Control and Prevention Lipids Standardization Program.¹⁶⁵

Cardiorespiratory Fitness. Maximal treadmill testing using a modified Balke protocol was used to assess CRF as treadmill time in minutes at baseline and during follow-up visits, as previously described.^{17, 21} Three CRF groups were created from age- and sex-specific quintiles based on the previously established cutpoints of treadmill time: low (bottom 20%), moderate (middle 50%), and high (top 20%) CRF.¹⁷ Change in CRF as a continuous variable was calculated as the difference in treadmill time between the first two successive examinations and divided by the number of years between them. Annual change in CRF was used to define change in fitness because the intervals between the follow-up examinations varied among individuals in ACLS. Change in CRF was categorized by grouping participants into categories of loss, stable, or gain, based on tertiles of change in CRF. For example, a participant categorized in the low CRF group at baseline that increased to the moderate CRF group at follow-up would be categorized in the gain group for CRF change.

Diet. Participants were asked to keep detailed records of everything they consumed over two pre-assigned weekdays and one weekend day for the 3-day dietary assessment. Written instructions on how to accurately describe foods and portion sizes were given to each participant. Registered dietitians at the Cooper Clinic coded and analyzed the diet records using the Cooper Clinic Nutrition and Exercise Evaluation system. Achievement of the AHA diet goals was categorized as follows: 4.5 or more servings of fruits and vegetables per day, two or more 3.5 oz. servings per week of fish, shellfish, or other seafood, three or more servings per day of whole grains, and less than 1500 mg per day of sodium. Diet scores

were assigned by giving a point for each diet goal met (i.e., consuming <1500 mg/day of sodium is one point) for a total possible score of four points.

Physical Activity. Participants completed a formerly validated questionnaire to assess leisure time PA over the past three months, which included type, frequency, and duration of activity. PA categories were created based on the responses for 10 specific activities: walking, jogging, running, treadmill exercise, cycling, stationary cycling, swimming, racquet sports, aerobic dance, and other sports related activities. The intensity of the activities was estimated using speed-specific or activity-specific metabolic equivalent (MET) values from the Compendium of Physical Activities.²² MET-minutes per week (min/wk) were then calculated by multiplying the MET value for each activity by frequency and duration. Then, MET-min/wk for all activities was added together. Participants were classified into three categories based on the 2008 Physical Activity Guidelines for Americans:²³ inactive (0 MET-min/wk), insufficient (1-499 MET-min/wk), and recommended (\geq 500 MET-min/wk).

AHA Ideal Cardiovascular Health. Each ideal CVH metric was classified as poor (0 points), intermediate (1 point), or ideal (2 points) as described in **Table 4.1**. The ideal CVH score was calculated on a 14-point scale and categorized as follows: inadequate (0-4 points), average (5-9 points), and optimum (10-14 points).

Annual change in total ideal CVH score as a discrete variable was calculated as the difference in total ideal CVH score between the two successive examinations, and divided by the number of years between them. Annual change

in total ideal CVH score was categorized by grouping participants into categories of loss, stable, or gain, based on tertiles of change as described above for change in CRF categories.

Statistical Analysis

Baseline characteristics were summarized for the total population and by sex. Differences between sexes at baseline were determined by t-tests for continuous variables and chi-square tests for categorical variables. Multivariable general linear and logistic regression models were used to evaluate the association of baseline CRF with baseline ideal CVH score and to estimate the odds of being in the average or optimum ideal CVH categories by baseline CRF categories, respectively. These cross-sectional analyses controlled for age, sex, and year of examination. To investigate the longitudinal association between changes in CRF and changes in ideal CVH, we employed linear regression models adjusting for age, sex, and time between exam dates. Separate models that included CRF and ideal CVH as either continuous or categorical variables were used. All models were performed in the total population and stratified by sex (removing sex as covariate in model). Finally, we conducted sensitivity analyses to examine the influence of each LS7 metric on total CVH score. No collinearity was observed after performing analyses to examine the influence of CRF on each of the LS7 metrics. SAS version 9.4 was used for all statistical analyses. The threshold for statistical significance was set at the $p < 0.05$ level.

RESULTS

Descriptive characteristics of the study population (n=11,590) are given in **Table 4.2**. The study population had a mean (standard deviation) age of 45.8 (9.8) years and BMI of 25.8 (4.1) kg/m². Males had higher baseline values for BMI, BP, total cholesterol, fasting plasma glucose, and treadmill time compared to females (p<0.0001). As shown in **Table 4.3**, the prevalence of participants from the total sample meeting ideal levels for each CVH metric at baseline was (in ascending order): healthy diet 4.3% (n=497), BP 33.0% (n=3,827), total cholesterol 45.9% (5,314), BMI 47.2% (n=5,473), smoking 56.2% (n=6,515), PA 59.9% (n=6,938), and fasting plasma glucose 61.9% (7,171). Only 0.24% of the total sample met ideal levels for all seven metrics at baseline.

Cross-sectional association of CRF and ideal CVH. Treadmill time was moderately correlated (p<0.0001) with CVH score in both males (r=0.56) and females (r=0.50). The prevalence of inadequate, average, and optimum categories for CVH score by baseline CRF category is displayed in **Figure 4.1**. For those in the low fitness group, only 10.8% were in the optimum category for ideal CVH score, while 17.1% were in the poor category. Conversely, only 0.4% of the high fit participants were in the poor category, while 54.2% achieved an optimum ideal CVH score.

In multivariable regression models, baseline treadmill time, sex, and age explained 15.2%, 14.3%, and 0.82% of the variance in total CVH score at baseline (all p<0.0001), respectively. After adjusting for age, sex, and year of examination, participants in the optimum CVH category had 20% and 43% higher

CRF levels than those in the average and inadequate CVH groups ($p < 0.0001$), respectively (**Figure 4.2**). The adjusted odds [shown as odds ratio (95% confidence interval)] of being in the average or optimum ideal CVH category were 10.9 (7.9-14.9) and 39.9 (28.7-55.4) times greater for individuals with moderate and high CRF, respectively, compared to those with low CRF ($p < 0.0001$) (**Figure 4.3**).

Longitudinal association of CRF and ideal CVH. The association between change in fitness and change in ideal CVH score was examined in 2,555 adults who had at least two clinic visits. After a mean follow up of 3.3 ± 2.4 years, the average change in ideal CVH score per year was $3.9 \pm 20.9\%$ and the average change in treadmill time per year was $1.2 \pm 9.2\%$ for the total sample. Annual change in ideal CVH score and annual change in treadmill time were positively correlated ($p < 0.0001$) in both males ($r = 0.40$) and females ($r = 0.26$).

After controlling for age, sex, and time between exam dates, the gain in fitness group ($n=851$) significantly ($p < 0.0001$) increased their ideal CVH score by $13.9 \pm 1.1\%$, while the loss of fitness group ($n=873$) significantly ($p < 0.0001$) decreased their score by $4.5 \pm 1.1\%$ (**Figure 4.4**). Baseline ideal CVH score and annual change in treadmill time explained 18.5% and 9.0% of the annual change in ideal CVH score, respectively, while changes in diet, cholesterol, smoking, diastolic BP, PA, glucose, BMI, and systolic BP explained 7.5%, 4.9%, 2.8%, 2.2%, 1.5%, 1.5%, 0.8%, and 0.4%, respectively ($p < 0.0001$ for all variables). For every minute increase in treadmill time per year, annual ideal CVH score significantly increased by 0.15 ± 0.01 ($p < 0.0001$).

Discussion

This study is likely the first to examine both cross-sectional and longitudinal associations of CRF with ideal CVH, as defined by the AHA's LS7, in middle-aged men and women. One of the main findings was that higher levels of CRF are strongly associated with better CVH profiles, which is demonstrated by moderate and high fit individuals having almost 11 and 40 times greater odds of having average or optimum CVH, respectively, compared to low fit individuals. In addition, our longitudinal analyses showed that improvements in CRF over time are independently associated with concomitant increases in CVH scores and these increases in CRF explained a greater amount of variance in CVH score compared to each of the individual LS7 metrics (blood cholesterol, fasting plasma glucose, BP, smoking, BMI, diet quality, and PA).

To date, the only study investigating the association between CRF and ideal CVH was completed in European adolescents aged 12.5-17.5 years enrolled in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study.¹⁶⁴ In this study, CRF was estimated via the 20m shuttle run test. The results from this study complement our findings in adults, as higher CRF levels were associated with a higher number of LS7 metrics at ideal levels in adolescents. CRF levels were significantly higher in both boys and girls that met at least four LS7 metrics at ideal levels. The results from the HELENA study and the present ACLS study show promising associations between CRF level and ideal CVH score in both adolescents and adults, thus warranting further investigation in differing populations.

In 2012, Yang *et al.* examined ideal CVH prevalence trends across the National Health and Nutrition Examination Survey (NHANES) in adult men and women from 1988 to 2010.¹³ The study found that the prevalence of meeting all LS7 metrics at ideal levels was low (only 1.2% in NHANES 2005-2010) and that ideal BMI and fasting plasma glucose levels continued to decline during the study period. The authors reported that the all-cause and CVD mortality benefits from improved smoking and PA metrics were counteracted by the low prevalence of BMI, diet, and plasma glucose at ideal conditions. As a moderator for these traditional CVD risk factors, CRF has been shown to beneficially alter the inhibitory effects of poor levels of the LS7 metrics on all-cause and CVD mortality.^{17, 50, 51} Our study found that having moderate to high levels of CRF greatly decreased the odds of having an inadequate CVH score. The importance of this prominent relationship is highlighted when examining the association between ideal CVH score and mortality risk. In NHANES, as the number of ideal LS7 metrics met increased, all-cause, CVD, and ischemic heart disease mortality rates significantly decreased.¹³ Therefore, even having a moderate level of CRF decreases the odds of having an inadequate CVH score, which in turn is likely related to decreased mortality rates. Thus, as mounting evidence strongly supports the benefits of high levels of CRF and PA on CVD risk factors and mortality,¹ our findings emphasize the potential importance of lifestyle interventions that include exercise/PA to improve both CRF and CVH status, strengthening the AHA's ideal CVH primordial prevention approach.

The present analyses benefited from several strengths of the ACLS study design. The ACLS cohort includes a relatively large number of participants enrolled in a prospective study with extensive follow-up. Participants underwent thorough medical examinations and maximal exercise tests, providing several valid, objective measures for some of the LS7 metrics and CRF at both baseline and follow-up (average time between exam dates was 3.3 years). We also excluded participants at baseline who had a history of CVD or cancer, who had a BMI $<18.5 \text{ kg/m}^2$, or who had abnormalities on electrocardiography, which reduced the likelihood of including participants who had underlying subclinical disease. Our study also has limitations to consider. The use of the AHA's ideal CVH construct to create the CVH score assumes that all LS7 health factors and behaviors equally contribute to the final score. To determine the relationship between CRF and ideal CVH score, CRF was entered into the model independently, but we acknowledge that each of the LS7 metrics have been found to be associated with CRF. However, our analyses did not demonstrate collinearity between CRF and the LS7 metrics. Additionally, the diet quality and PA LS7 metrics in our study relied on self-report data, which can introduce biases. The instruments and procedures utilized were standardized and validated in order to minimize the effect of bias. Furthermore, compared with the AHA definition of ideal CVH, we made minor adjustments to assessing diet quality, smoking status, and medication use. There was insufficient information to include sugar-sweetened beverages in assessing diet components, as well as lack of information regarding the length of time since a former smoker had quit.

Conclusion

Our study found that higher levels of CRF are associated with better CVH profiles in both men and women. In addition, improving CRF during middle age was independently associated with higher CVH scores and greater improvement in CVH. Our findings support future research regarding the use of exercise interventions as a primordial prevention to not only improve CRF, but also to improve and maintain ideal CVH to achieve the AHA 2020 Impact Goals and reduce the burden of CVD in America.

Table 4.1. Definition of poor, intermediate, and ideal levels for each cardiovascular health metric^a

Cardiovascular Health Metric	Poor (0)	Intermediate (1)	Ideal (2)
Smoking	Current	Former	Never
Body mass index (kg/m ²)	≤30	25-29.9	18.5-24.9
Physical activity (MET-min/week)	0	1-499	≥500
Healthy diet score (No. of components)	0-1	2	3-4
Total cholesterol (mg/dL)	≥240	200-239	<200
Blood pressure (mmHg)	SBP ≥140 or DBP ≥90	SBP 120-139 or DBP 80-89	SBP <120 and DBP <80
Fasting plasma glucose (mg/dL)	≥126	100-125	<100

MET: metabolic equivalent; SBP: systolic blood pressure; DBP: diastolic blood pressure

^a SI conversion factors: to convert total cholesterol values from mg/dL to mmol/L, multiply by 0.0259; to convert fasting plasma glucose values from mg/dL to mmol/L, multiply by 0.0555

^b Plus no previous physician diagnosis of hypercholesterolemia

^c Plus no previous physician diagnosis of hypertension

^d Plus no previous physician diagnosis of diabetes or use of insulin

Table 4.2. Baseline characteristics by sex

Variable	All (n=11,590)	Males (n=8,865)	Females (n=2,725)
Age (years)	45.8 (9.8)	46.2 (9.7)	44.8 (10.0)
Body mass index (kg/m ²)	25.8 (4.1)	26.5 (3.7)	23.5 (4.4)
Systolic blood pressure (mmHg)	119.4 (13.9)	121.6 (13.1)	112.1 (13.8)
Diastolic blood pressure (mmHg)	80.1 (9.8)	81.5 (9.4)	75.4 (9.4)
Total cholesterol (mg/dL)	206.6 (39.9)	208.6 (40.0)	199.7 (39.2)
Fasting plasma glucose (mg/dL)	98.8 (16.1)	100.1 (15.5)	94.7 (17.2)
Treadmill time (min)	18.1 (5.2)	19.2 (4.9)	14.5 (4.6)

Data presented as mean (SD)

P-value for difference between sexes < 0.0001 for all variables

Table 4.3. Prevalence of participants meeting ideal levels for each cardiovascular health metric at baseline in the total population and by sex

Cardiovascular health metric at ideal level	All (n=11,590)	Males (n=8,865)	Females (n=2,725)
Smoking*	56.2	53.5	65.0
Body mass index*	47.2	38.7	75.1
Physical activity	59.9	59.7	60.4
Diet*	4.3	4.6	3.4
Total cholesterol*	45.9	43.3	54.3
Blood pressure*	33.0	25.8	56.4
Fasting plasma glucose*	61.9	56.9	78.0
All seven metrics at ideal level	0.24	0.17	0.48

Data presented as percentage

*Significantly different between sexes ($p < 0.0001$)

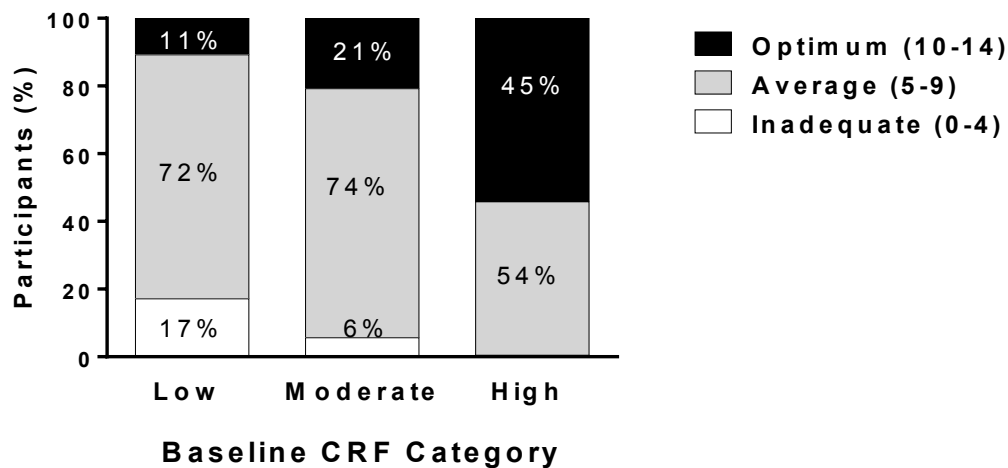


Figure 4.1. Prevalence of inadequate, average, and optimum scores for cardiovascular health by baseline fitness category.

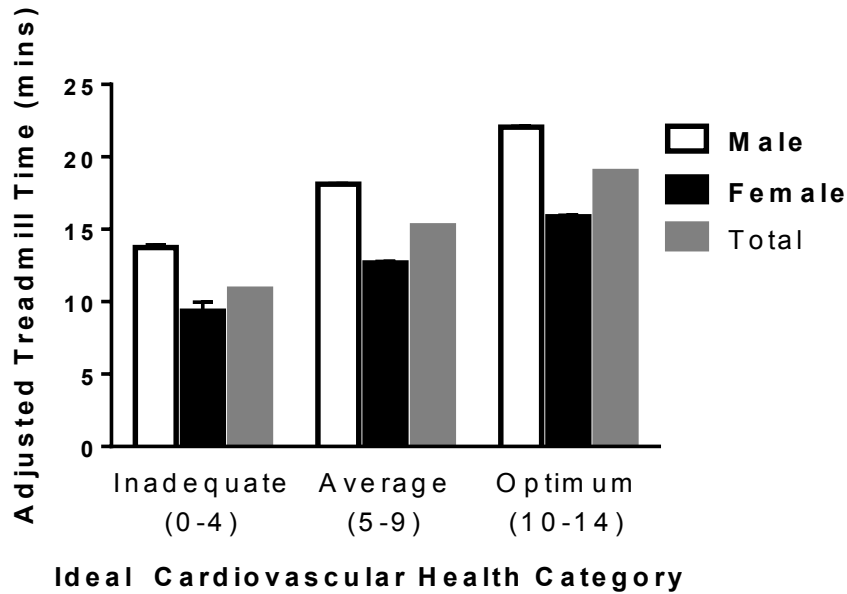


Figure 4.2. Average treadmill time in the total population and by sex based on ideal cardiovascular health category. Values adjusted for age and year of examination. $p < 0.0001$ for all group and sex comparisons.

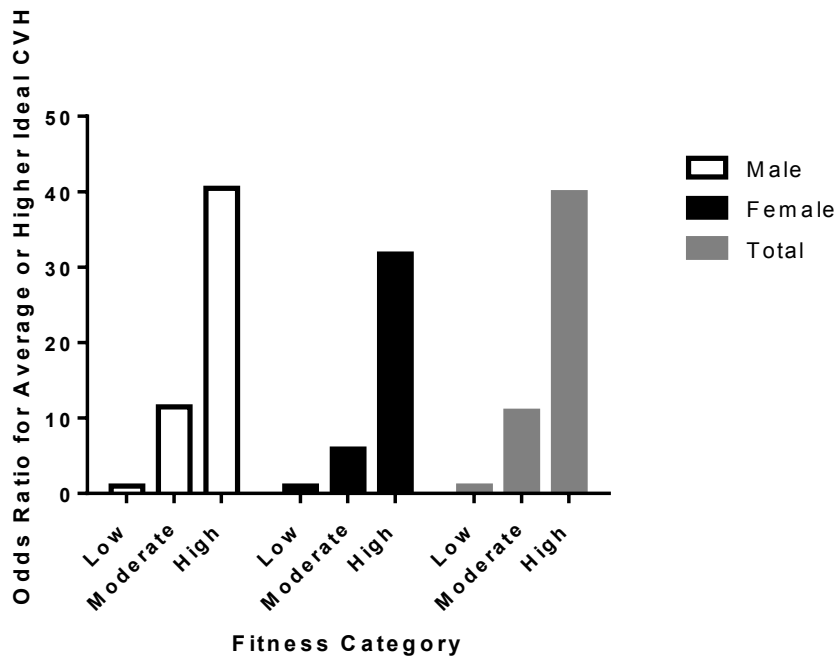


Figure 4.3. Adjusted odds of being in the average or higher ideal cardiovascular health category by baseline fitness category. Values adjusted for age and year of examination. $p < 0.0001$ for all group and sex comparisons.

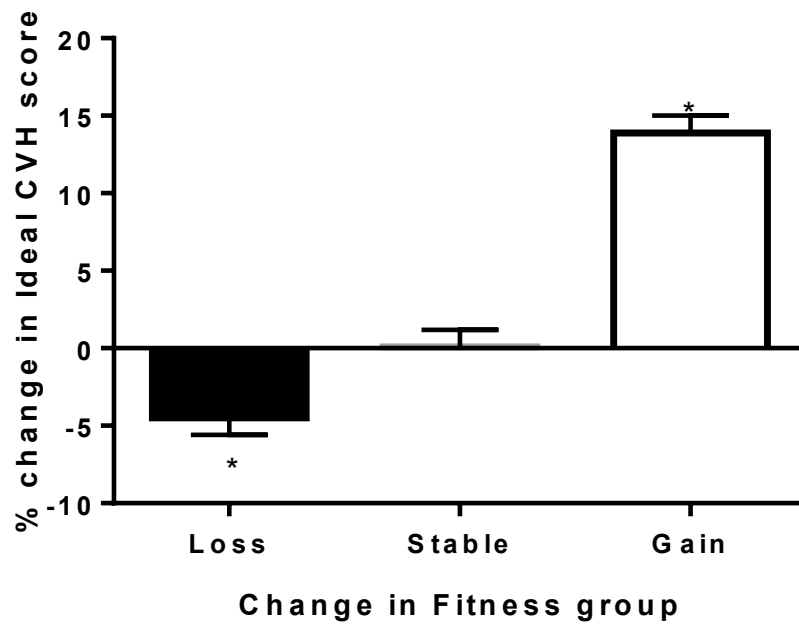


Figure 4.4. Percent change in ideal cardiovascular health score by change in fitness group. Values adjusted for age, sex, and time between exam dates. * $p < 0.0001$ for difference with all other groups

CHAPTER 5

CARDIORESPIRATORY FITNESS AND CARDIOMETABOLIC DISEASE RISK FACTOR RESPONSIVENESS FOLLOWING AEROBIC EXERCISE INTERVENTION

INTRODUCTION

Cardiorespiratory fitness (CRF) is well established as having a strong inverse association with numerous cardiometabolic disease risk factors and cardiovascular disease (CVD) mortality.¹ As CVD remains the number one cause of death in America,² the detrimental effects of low CRF present a substantial health threat. In order to help combat these detrimental effects, aerobic exercise interventions are used to increase CRF, as measured by maximal oxygen uptake ($\dot{V}O_{2max}$), and improve cardiometabolic risk factor profile. However, considerable inter-individual variation exists in the ability to improve $\dot{V}O_{2max}$ and cardiometabolic risk factors in response to regular exercise.¹⁶⁶⁻¹⁷² Thus, identifying individuals who do not experience significant gains in CRF with aerobic training (i.e., low $\dot{V}O_{2max}$ response) and how low $\dot{V}O_{2max}$ response relates to risk factor responsiveness is of great interest. As we move further into the era of personalized medicine, a better understanding of the inter-individual variation in response to regular exercise will enhance our ability to utilize exercise as

medicine and provide appropriate guidance to improve health and attenuate CVD risk.

The HEalth, RIsk factors, exercise Training And GENetics (HERITAGE) family study has been instrumental in the development of the strong body of evidence supporting the presence of heterogeneous $\dot{V}O_{2\max}$ and cardiometabolic risk factor responsiveness to exercise training.^{166-168, 173, 174} Although several exercise training studies have reported the *distribution* of $\dot{V}O_{2\max}$ responsiveness to standardized exercise interventions,^{166, 169, 171, 172, 174-180} the *prevalence* of individuals experiencing low $\dot{V}O_{2\max}$ responsiveness remains unknown as there is currently no widely accepted threshold to define $\dot{V}O_{2\max}$ responsiveness. Thus, the goal of the present study was to establish cutpoints to identify low $\dot{V}O_{2\max}$ response and examine the prevalence of low $\dot{V}O_{2\max}$ response across several diverse exercise interventions. We also sought to examine the relationship between $\dot{V}O_{2\max}$ responsiveness and exercise-induced changes in cardiometabolic risk factors.

METHODS

The effects of standardized, supervised aerobic exercise training on $\dot{V}O_{2\max}$ and cardiometabolic risk factor responsiveness was examined across eight exercise training studies comprised of 14 distinct exercise interventions. The studies are briefly described below, followed by the definitions of low response for each trait and the statistical procedures employed. Overall, the exercise interventions from these studies ranged from doses of 4-35 kcal·kg⁻¹·week⁻¹ (KKW); intensities of 50-85% $\dot{V}O_{2\max}$; and durations of 16-35 weeks.

Study-specific exercise intervention information is shown in **Table 5.1**. Data on a maximum of 1,724 adults who completed one of the 14 exercise interventions were available for analysis.

Exercise Training Studies

Dose-Response to Exercise in Women (DREW) study. The DREW Study was a randomized controlled dose-response exercise trial. A complete description of the design, methods, and study participants has been published.^{24, 173} The present cohort included 361 previously sedentary, post-menopausal, overweight or obese women (63% White) with high-normal blood pressure who completed one of three 24-week aerobic exercise interventions. The three exercise interventions were designed for participants to expend 4 (n=155), 8 (n=104), or 12 (n=102) KKW. All participants alternated training sessions on a cycle ergometer or treadmill with a target intensity of 50% $\dot{V}O_{2max}$. Exercise training sessions were completed three to four times per week.

Gene Exercise Research Study (GERS). The GERS cohort included 171 previously sedentary, non-diabetic, non-smoking men and women (56%) aged 50-71 years (73% White). Participants had no history of CVD, had a BMI <37 kg/m², and were either normotensive or had medication-controlled hypertension. The exercise intervention consisted of 24 weeks (three sessions per week) of aerobic exercise. Training progressed to a target exercise intensity of 70% $\dot{V}O_{2max}$.^{26, 27} Participants used various types of aerobic exercise equipment including cycle ergometers, treadmills, rowers, and elliptical, skier, and stepping machines.²⁵

HERITAGE Family Study. The HERITAGE cohort included 718 (66% White) men and women (56%) aged 17-65 years who completed a 20-week aerobic exercise intervention. Participants were previously sedentary, normotensive to untreated mildly hypertensive, and had a body mass index (BMI) $<40.0 \text{ kg/m}^2$. The intervention consisted of aerobic exercise performed three days per week on a cycle ergometer. Training progressed to a target exercise intensity of $75\% \dot{V}O_{2\text{max}}$.²⁸

Energy Flux study. The Energy Flux Study was a randomized controlled exercise trial that included 64 men and women (45%) aged 21-45 years (48% White) who completed one of two 24-week aerobic exercise interventions. Participants were previously sedentary, generally healthy adults with a BMI of $25\text{-}35 \text{ kg/m}^2$. The two exercise interventions were designed for participants to expend 17.5 (n=33) or 35 (n=31) KKW. Training progressed to a target exercise intensity of 70-75% maximal heart rate. One month and three months into the intervention, participants performed additional maximal exercise tests. Exercise intensity was adjusted throughout the intervention based on the most recent maximal exercise test. All exercise was performed on a treadmill 3-6 times per week.

Inflammation and Exercise (INFLAME) study. The INFLAME cohort included 66 previously sedentary, generally healthy, non-smoking men and women (65%) with elevated plasma C-Reactive Protein concentration ($\geq 2.0 \text{ mg/L}$ but $<10.0 \text{ mg/L}$) who completed a 16-week aerobic exercise intervention. At baseline, participants (65% White) were aged 30-75 years with a BMI 18-40

kg/m², and blood pressure <140/90 mmHg. The exercise intervention was designed for participants to expend 16 KKW at a target exercise intensity 60-80% $\dot{V}O_{2max}$. Exercise was performed on either a treadmill or cycle ergometer 3-5 times per week.²⁹

Examination of Mechanisms of Exercise-induced Weight Compensation (E-MECHANIC) study. E-MECHANIC was a six-month randomized controlled exercise trial, which included 117 men and women (72%) who completed one of two aerobic exercise interventions. Participants (68% White) were non-smoking, generally healthy, previously sedentary adults (aged 18-65 years) with a BMI of 25-45 kg/m². The two exercise interventions were designed for participants to expend 8 (n=60) or 20 (n=57) KKW for 24 weeks. All exercise was performed on a treadmill at a target intensity of 65-85% $\dot{V}O_{2max}$. Exercise sessions were completed 3-5 times per week.³⁰

Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE). The STRRIDE I³¹ and II³² studies were randomized exercise trials. The present cohort included 227 (83% White) non-smoking men and women (50%) who completed eight months of exercise training. Participants were free of diabetes and coronary artery disease, aged 40-65 years with a BMI 25-35 kg/m², resting blood pressure <160/90 mmHg, and mild-to-moderate dyslipidemia [low-density lipoprotein cholesterol (LDL-C) 130-190 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) 40mg/dL (men) or 45 mg/dL (women)]. Combining STRRIDE I and II, participants completed one of four exercise interventions: mild (14 KKW; 40-55% $\dot{V}O_{2peak}$; n=36), moderate (14

KKW; 65-80% $\dot{V}O_{2peak}$; n=90), high (23 KKW; 65-80% $\dot{V}O_{2peak}$; n=57), or moderate plus resistance training (three days per week, three sets per day, and 8-12 repetitions per set; n=44). Aerobic exercise was performed three times per week on treadmills, elliptical machines, or cycle ergometers.

Measurements of Cardiorespiratory Fitness and Cardiometabolic Risk Factors

All participants underwent multiple laboratory measures at baseline and post-training. Full details for each of the studies are available elsewhere.²⁴⁻³² Briefly, all studies objectively measured $\dot{V}O_{2max}$ with gas exchange during graded maximal exercise testing. Blood pressure was measured after participants sat quietly for at least five minutes. Blood samples were obtained from venipuncture of an antecubital vein in the morning following an overnight fast. Post-training blood samples were obtained approximately 16-72 hours after the completion of the final exercise session. All studies included plasma measures of HDL-C and triglycerides (TG) via enzymatic methods except for STRRIDE I and II, which assessed HDL-C and TG concentrations via nuclear magnetic resonance spectroscopy. Plasma fasting insulin was assessed in all studies except Energy Flux, E-MECHANIC, and STRRIDE II. Plasma fasting insulin was measured by radioimmunoassay in GERS and HERITAGE, by immunoassay in STRRIDE I, and by electrochemiluminescence in DREW and INFLAME. For each of these traits, change (Δ) was calculated as the post-training value minus the baseline value. Subsequently, the change values were used to determine responsiveness of each trait based upon the following definitions.

Definition of Low Responses

In order to define low responsiveness, technical error (TE) was used to define the threshold values for each trait. TE is defined as the within-subject standard deviation (SD) from repeated measures over a given period of time, which takes into account the measurement error of the trait, including the variance among laboratories or laboratory technicians, and the normal daily biological variability of the trait. For this study, the definition of low response for each trait was based on previous findings from reproducibility studies conducted in HERITAGE.³⁷⁻⁴¹ These studies were designed to quantify TE, coefficient of variation (CV), and intraclass correlation for several traits measured in HERITAGE. Based on the TE and CV values derived from these studies, low $\dot{V}O_{2\max}$ response was defined in both absolute (gain <120 ml/min from baseline value) and relative (gain < 5% of study-specific baseline average $\dot{V}O_{2\max}$ in $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) terms. In regards to each of the cardiometabolic risk factors, any value beyond 1xTE in a direction indicating a worsening of the risk factor was considered a low response. Accordingly, the threshold values to determine low response were: Δ plasma fasting insulin ≥ 12 pmol/L; Δ plasma HDL-C ≤ 0.12 mmol/L; Δ plasma TG ≥ 0.21 mmol/L; and Δ resting systolic blood pressure (SBP) ≥ 5 mmHg.

Statistical Analysis

Baseline characteristics were summarized for the total population and by study. Prevalence of low response for each trait was assessed on the basis of the number of participants who exceeded the 1xTE threshold defined above. For

each of the cardiometabolic risk factors, a logistic regression was performed to compare the distribution of low response between $\dot{V}O_{2\max}$ response groups. A total response score for all of the cardiometabolic risk factors was calculated for each participant. Each risk factor classified as a low response received a score of one, while each risk factor not classified as a low response received a score of zero. Thus, a participant that displayed low responses for all risk factors would receive four total points for their cardiometabolic risk factor response score. A chi-square test was performed to compare the distribution of the total response score between $\dot{V}O_{2\max}$ response groups. The threshold for statistical significance was set at $p < 0.05$. SAS version 9.4 was used for all statistical analyses. Data presented as mean (SD) unless otherwise specified.

RESULTS

The overall sample ($n=1,724$) was comprised of 63.6% women, 29.2% minorities, and broad ranges of age (17-75 years), BMI ($18-45 \text{ kg/m}^2$), and cardiometabolic risk factors. Study-specific baseline characteristics of the participants are summarized in **Table 5.2**.

The majority of the exercise interventions produced significant group mean increases in $\dot{V}O_{2\max}$ (data not shown). All interventions except INFLAME and DREW 4, 8, and 12 KKW produced significant group mean increases in absolute $\dot{V}O_{2\max}$ ($p < 0.05$). For relative $\dot{V}O_{2\max}$, all interventions except E-MECHANIC 8 KKW and INFLAME produced significant group mean increases ($p < 0.05$). Upon evaluation of individual changes in $\dot{V}O_{2\max}$ using the above definitions, 34% (absolute; individual distribution shown in **Figure 5.1**) and 23.8%

(relative; individual distribution not shown) of the total sample was considered low responsive for $\dot{V}O_{2\max}$. Within each exercise intervention group, the prevalence of individuals with a low $\dot{V}O_{2\max}$ response varied greatly, ranging from 7.6% (HERITAGE) to 84% (DREW 4 KKW) based on the absolute definition of responsiveness (**Figure 5.2a**). As shown in Figure **5.2b**, a wide range of low $\dot{V}O_{2\max}$ response prevalence was also present based on the relative definition of responsiveness, from 7.4% (HERITAGE) to 68.2% (INFLAME).

Since the threshold for relative $\dot{V}O_{2\max}$ responsiveness was based upon study-specific values, the prevalence of low $\dot{V}O_{2\max}$ response in relative terms was further explored by comparing groups within studies that employed multiple exercise interventions. Within the DREW study, exercise intensity and intervention duration were equivalent amongst the exercise groups. As exercise dose increased from 4 to 8 to 12 KKW, the prevalence of relative $\dot{V}O_{2\max}$ low response decreased from 53.1% to 37.1% to 30.5% ($p=0.001$ for difference between groups). Similarly, in the E-MECHANIC study relative $\dot{V}O_{2\max}$ low response prevalence was lower in the 20 KKW group (26.3%) compared to the 8 KKW group (50%) ($p=0.009$). Although not statistically significant ($p=0.16$), the Energy Flux study also demonstrated an inverse relationship between relative $\dot{V}O_{2\max}$ low response prevalence and exercise dose (51.5% for the 17.5 KKW group and 34.4% for the 35 KKW group). All of the STRRIDE interventions were delivered for 35 weeks, but differed in both exercise amount and intensity. The prevalence of low $\dot{V}O_{2\max}$ response followed the same trend as described above: as exercise amount and intensity increased, prevalence of low $\dot{V}O_{2\max}$ response

decreased (55.6% for 14 KKW at 40-55% intensity compared to 14% for 23 KKW at 65-80% intensity, $p < 0.0001$ for differences between groups). These results for studies employing multiple exercise interventions are illustrated in **Figure 5.3**.

Table 5.3a and **Table 5.3b** show the average change for the selected cardiometabolic risk factors in all exercisers combined and by $\dot{V}O_{2\max}$ response groups. Overall, fasting plasma insulin, HDL-C, TG, and resting SBP changed by -5.39 (25.71) pmol/L, 0.01 (0.17) mmol/L, -0.07 (0.45) mmol/L, and -0.55 (10.43) mmHg, respectively. There were no differences in the mean values for exercise-induced change in the four cardiometabolic traits between absolute or relative $\dot{V}O_{2\max}$ response groups. For the combined sample, prevalence of low response of the cardiometabolic traits ranged from 19.6% for plasma fasting insulin to 61.7% for plasma HDL-C. For absolute low $\dot{V}O_{2\max}$ responders, the prevalence of low response was 7.5%, 22.9%, 8.1%, and 10.1% for plasma fasting insulin, HDL-C, TG, and resting SBP, respectively (**Table 5.3a**). Evaluation of low risk factor response on the basis of relative terms for low $\dot{V}O_{2\max}$ response resulted in lower prevalence values: 5.1%, 16.3%, 5.3%, and 7.6% for plasma fasting insulin, HDL-C, TG, and resting SBP, respectively (**Table 5.3b**). **Figures 5.4a, 5.4b, 5.4c, and 5.4d** illustrate the prevalence of low response for fasting plasma insulin, HDL-C, TG, and resting SBP, respectively, by relative $\dot{V}O_{2\max}$ response groups in the combined sample. The prevalence of low response for each cardiometabolic risk factor did not differ based on relative $\dot{V}O_{2\max}$ response groups.

A total risk factor response score was calculated for 1,081 participants with complete risk factor response data (i.e., baseline and post-training measures for all four cardiometabolic risk factors). Overall, the prevalence of scores was 20.1%, 41.1%, 26.5%, 10.9%, and 1.5% for scores of 0, 1, 2, 3, and 4, respectively. **Figure 5.5a** illustrates the distribution of total risk factor response scores by absolute $\dot{V}O_{2\max}$ response groups (significantly different between groups, $p < 0.01$), while **Figure 5.5b** displays the total risk factor response score distribution by relative $\dot{V}O_{2\max}$ response groups (significantly different between groups, $p < 0.01$). The distribution of total risk factor response score was assessed amongst low $\dot{V}O_{2\max}$ responders ($n=241$). Based on absolute $\dot{V}O_{2\max}$ terms, the prevalence of scores was 12.5%, 39.4%, 33.4%, 13.6%, and 1.1% for scores of 0, 1, 2, 3, and 4, respectively (**Figure 5.6a**). When assessing the distribution of total risk factor response score amongst relative low $\dot{V}O_{2\max}$ responders ($n=241$), only one participant received a score of 4, while 53.1% received a score of 1 or lower (**Figure 5.6b**).

DISCUSSION

This study is likely the first to evaluate the prevalence of $\dot{V}O_{2\max}$ low response across diverse populations and varying exercise interventions. This study found a high prevalence of $\dot{V}O_{2\max}$ low response across 14 diverse exercise interventions, which differed based on how low response was defined (34% relative; 24% relative). We also found that the prevalence of low response for the cardiometabolic risk factors following exercise training varied from 19.6% for changes in fasting insulin to 61.7% for changes in HDL-C. Despite the high

prevalence of low response observed across all studies, the likelihood of being a low responder for all traits ($\dot{V}O_{2\max}$, fasting insulin, HDL-C, TG, and SBP) was extremely low, as only one participant out of 1,081 (0.1%) did not demonstrate exercise training-induced changes below the low response threshold for these traits. As the majority of participants demonstrated a total risk factor response score of 1 or lower whether they were a relative low $\dot{V}O_{2\max}$ responder (53.1%) or not (63.5%), our results reinforce the idea that regular exercise participation is associated with many health benefits, regardless of the presence of a detectable $\dot{V}O_{2\max}$ response.

A recent study reported on the *adverse* responsiveness of cardiometabolic risk factors (plasma fasting insulin, plasma HDL-C, plasma TG, and resting SBP) to exercise training in many of the same studies included in the present report.⁴² Based on reproducibility studies from HERITAGE, adverse responses were defined as two times the TE in a direction signifying a worsening of the risk factor. Similar to our study's low response prevalence, Bouchard and colleagues⁴² found that only a small minority of participants (<1%) exhibited adverse responses for three or more traits. Although some participants experienced undesirable responses for select risk factors, their results align with the present study as the majority of participants do not demonstrate a worsening of their cardiometabolic risk factor profile.⁴²

The HERITAGE study demonstrated the smallest prevalence of low $\dot{V}O_{2\max}$ response, which was to be expected as both the absolute and relative cutpoints for low $\dot{V}O_{2\max}$ response were derived from TE and CV values from the

HERITAGE reproducibility studies.³⁷ Conversely, the DREW study demonstrated the highest prevalence of low $\dot{V}O_{2\max}$ response in absolute terms (83.9%), while the INFLAME study had the greatest relative $\dot{V}O_{2\max}$ low response prevalence (68.2%). Although there was not a clear trend related to exercise dose, intensity, or program duration when comparing low $\dot{V}O_{2\max}$ response across all interventions, a trend emerged when exploring the relative $\dot{V}O_{2\max}$ responsiveness within studies that employed multiple exercise interventions/doses. As demonstrated by the DREW, E-MECHANIC, Energy Flux, and STRRIDE studies, as exercise dose and/or intensity increased, prevalence of low $\dot{V}O_{2\max}$ response decreased. This finding is comparable to a study conducted by Ross and colleagues that was designed to assess the separate effects of exercise intensity and amount on $\dot{V}O_{2\max}$ responsiveness.¹⁶⁹ In this study, participants (n=121 middle-aged men and women) were randomized to one of three exercise groups: low amount and low intensity, high amount and low intensity, or high amount and high intensity. Results demonstrated that increasing either the intensity or the amount of exercise substantially reduced the rate of $\dot{V}O_{2\max}$ non-response (defined as a change within 1xTE). When comparing exercise groups of the same intensity, the rate of non-response was reduced by about half when the amount of exercise doubled. Furthermore, when comparing groups with a fixed amount of exercise, there was no apparent $\dot{V}O_{2\max}$ non-response when exercise intensity was at 75% $\dot{V}O_{2\text{peak}}$.¹⁶⁹

A recent report by Montero and Lundby further investigated this dose-response relationship in a short-term exercise training study (n=78 young, healthy males).¹⁸¹ At the completion of a six-week exercise intervention, participants classified as CRF non-responders completed a successive six-week training program that included two additional exercise sessions per week. Non-responses were defined as any change in CRF, determined by maximal incremental exercise power output, within the typical error of measurement ($\pm 3.96\%$). Upon completion of the second exercise intervention, prevalence of non-response was eliminated. Although the findings were limited to a sample of healthy young males who completed only 12 total weeks of exercise, the authors concluded that increasing the dose of exercise in a repeated exercise intervention could abolish CRF non-response.¹⁸¹ We do not know whether low responders in a different population with additional risk factors, like the present study includes, would improve their responsiveness if they were exposed to different exercise doses. However, the work by Montero and Lundby offers promising insight for future research in this area.

The present study benefited from several strengths. The 14 distinct, randomized, and supervised exercise interventions included in this study provided a unique opportunity to investigate the heterogeneity of response to regular exercise across varying exercise interventions and a diverse population. The exercise interventions ranged from doses of 4-35 KKW, intensities of 50-85% $\dot{V}O_{2max}$, and durations of 16-35 weeks. Our large sample of 1,724

participants included 63.6% women, 29.2% minorities, and broad ranges of age, body weight, and cardiometabolic risk factors.

We realize our approach for establishing $\dot{V}O_{2\max}$ low response cutpoints has limitations. We acknowledge that the situation becomes more complicated when we apply the observed TE from one study (HERITAGE) to other exercise interventions that differ in terms of population and exercise programming. We also recognize this limitation remains consistent amongst the evaluation of low response prevalence for each cardiometabolic risk factor. However, to calculate study-specific TE, performing multiple measurement visits, including maximal exercise tests and blood samples, at both baseline and post-intervention presents a substantial burden. Thus, our results underscore the need for further investigation to refine the process for identification of individuals who are low responders to exercise training.

Conclusion

Our study found a substantial range of individual variability that occurred in response to regular exercise training. This heterogeneous display of individual responsiveness was present for all traits across all studies. Although there was substantial prevalence of low response for $\dot{V}O_{2\max}$, fasting insulin, HDL-C, TG, and resting SBP at the study level, our findings indicated that less than 1% of participants were low responders for all traits. Future research can aid in the refinement of these cutpoints to establish a suitable quantification of low response. These findings will facilitate the identification of individuals who

respond unfavorably to an exercise intervention and subsequent adjustment of their exercise prescription to maximize clinically important health outcomes.

Table 5.1. Study-specific exercise intervention information

	DREW			GERS	HERITAGE	Energy Flux	
Sample Size (n)	155	104	102	171	718	33	31
Exercise Dose (KKW)	4	8	12	~10-12	~12-14	17.5	35
Exercise Intensity (%)	50	50	50	70	75	70-75	70-75
Duration (weeks)	24	24	24	24	20	24	24
	INFLAME			E-MECHANIC		STRIDE I and II	
Sample Size (n)	66	60	57	36	90	57	44
Exercise Dose (KKW)	16	8	20	14	14	23	14
Exercise Intensity (%)	60-80	65-85	65-85	40-55	65-80	65-80	65-80
Duration (weeks)	16	24	24	35	35	35	35

Table 5.2. Baseline characteristics by study

	DREW	GERS	HERITAGE	E. Flux	INFLAME	E-MECH	STRIDE
Sample Size	361	171	718	64	66	117	227
Female (%)	100	55.6	56.1	45.3	65.2	71.8	49.8
White (%)	63	73.1	65.9	48.4	65.2	67.5	83.3
Age (years)	57.3 (6.6)	58.1 (5.7)	35.0 (13.6)	31.2 (7.3)	50 (11.4)	47.8 (11.9)	50.7 (8.0)
Weight (kg)	84.1 (11.6)	81.4 (15.0)	75.9 (17.2)	82.2 (13.5)	90.7 (15.5)	87.3 (16.0)	88.3 (13.0)
BMI (kg/m ²)	31.6 (3.8)	28.3 (4.3)	26.5 (5.3)	28.0 (2.9)	31.4 (3.6)	31.3 (4.7)	30.2 (3.1)
Body Fat (%)	28.3 (4.4)	36.3 (9.3)	27.8 (10.3)	34.8 (7.2)	39.0 (6.7)	N/A	N/A
SBP (mmHg)	138.8 (13.3)	131.7 (15.6)	118.4 (11.7)	125.2 (10.5)	132.8 (18.4)	120.1 (10.3)	125.2 (15.1)
DBP (mmHg)	80.8 (8.7)	85.2 (10.2)	68.1 (8.8)	77.9 (7.2)	80.3 (10.2)	77.1 (7.3)	81.8 (8.9)
HDL-C (mmol/L)	1.5 (0.4)	1.2 (0.4)	1.1 (0.3)	1.3 (0.4)	1.3 (0.3)	1.5 (0.4)	1.3 (0.4)
TG (mmol/L)	1.8 (6.2)	1.7 (1.1)	1.3 (0.7)	1.0 (0.5)	1.3 (0.5)	1.3 (0.6)	1.1 (1.1)
Insulin (pmol/L)	73.1 (40.9)	81.4 (29.6)	70.1 (48.7)	N/A	98.1 (48.0)	N/A	65.3 (41.5)
$\dot{V}O_{2max}$ (mL·kg ⁻¹ ·min ⁻¹)	15.3 (3.1)	25.2 (4.7)	31.2 (8.8)	29.5 (7.5)	18.7 (5.5)	23.8 (5.3)	28.2 (5.8)

Table 5.3a. Mean change and prevalence of low response for each cardiometabolic risk factor by absolute $\dot{V}O_{2\max}$ response group

	All Exercisers	Low $\dot{V}O_{2\max}$ Responders ^a	$\dot{V}O_{2\max}$ Responders
Δ Plasma Fasting Insulin			
Mean (SD) Change (pmol/L)	-5.39 (25.71)	-3.75 (28.50)	-6.22 (24.2)
Low Responders ^b (n, %)	242 (19.6)	92 (7.5)	150 (12.2)
Δ Plasma HDL-C			
Mean (SD) Change (mmol/L)	0.01 (0.17)	-0.02 (0.19)	0.03 (0.15)
Low Responders ^c (n, %)	961 (61.7)	356 (22.9)	605 (38.9)
Δ Plasma TG			
Mean (SD) Change (mmol/L)	-0.07 (0.45)	-0.06 (0.46)	-0.07 (0.45)
Low Responders ^d (n, %)	357 (23.4)	124 (8.1)	233 (15.3)
Δ Resting SBP			
Mean (SD) Change (mmHg)	-0.55 (10.43)	-0.71 (12.19)	-0.47 (9.43)
Low Responders ^e (n, %)	430 (26.6)	164 (10.1)	266 (16.5)

^a $\Delta \dot{V}O_{2\max} < 120$ mL/min; ^b Δ plasma fasting insulin ≥ 12 pmol/L; ^c Δ plasma HDL-C ≤ 0.12 mmol/L; ^d Δ plasma triglycerides ≥ 0.21 mmol/L; ^e Δ systolic blood pressure ≥ 5 mmHg; no significant differences were found for mean changes between absolute $\dot{V}O_{2\max}$ response groups

Table 5.3b. Mean change and prevalence of low response for each cardiometabolic risk factor by relative $\dot{V}O_{2\max}$ response group

	All Exercisers	Low $\dot{V}O_{2\max}$ Responders ^a	$\dot{V}O_{2\max}$ Responders
Δ Plasma Fasting Insulin			
Mean (SD) Change (pmol/L)	-5.39 (25.71)	-4.65 (28.40)	-5.61 (24.89)
Low Responders ^b (n, %)	242 (19.6)	63 (5.1)	179 (14.5)
Δ Plasma HDL-C			
Mean (SD) Change (mmol/L)	0.01 (0.17)	-0.01 (0.17)	0.02 (0.16)
Low Responders ^c (n, %)	961 (61.7)	253 (16.3)	708 (45.5)
Δ Plasma TG			
Mean (SD) Change (mmol/L)	-0.07 (0.45)	-0.05 (0.46)	-0.07 (0.45)
Low Responders ^d (n, %)	357 (23.4)	81 (5.3)	276 (18.1)
Δ Resting SBP			
Mean (SD) Change (mmHg)	-0.55 (10.43)	-0.51 (12.54)	-0.56 (9.68)
Low Responders ^e (n, %)	430 (26.6)	123 (7.6)	307 (19.0)

^a $\Delta < 5\%$ of study-specific baseline average $\dot{V}O_{2\max}$; ^b Δ plasma fasting insulin ≥ 12 pmol/L; ^c Δ plasma HDL-C ≤ 0.12 mmol/L; ^d Δ plasma triglycerides ≥ 0.21 mmol/L; ^e Δ systolic blood pressure ≥ 5 mmHg; no significant differences were found for mean changes between relative $\dot{V}O_{2\max}$ response groups

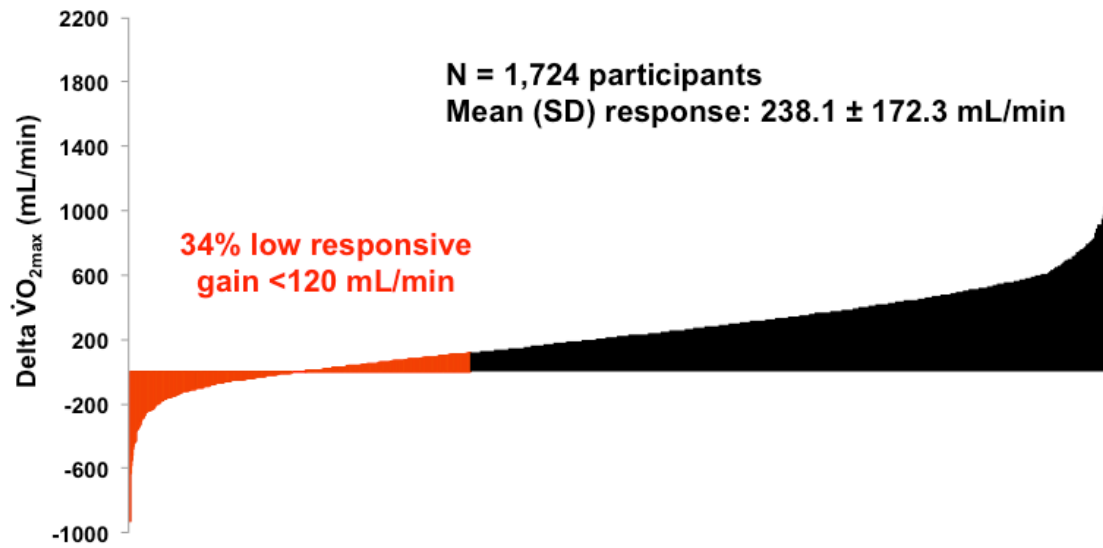


Figure 5.1. Distribution of absolute $\dot{V}O_{2\max}$ training response across studies

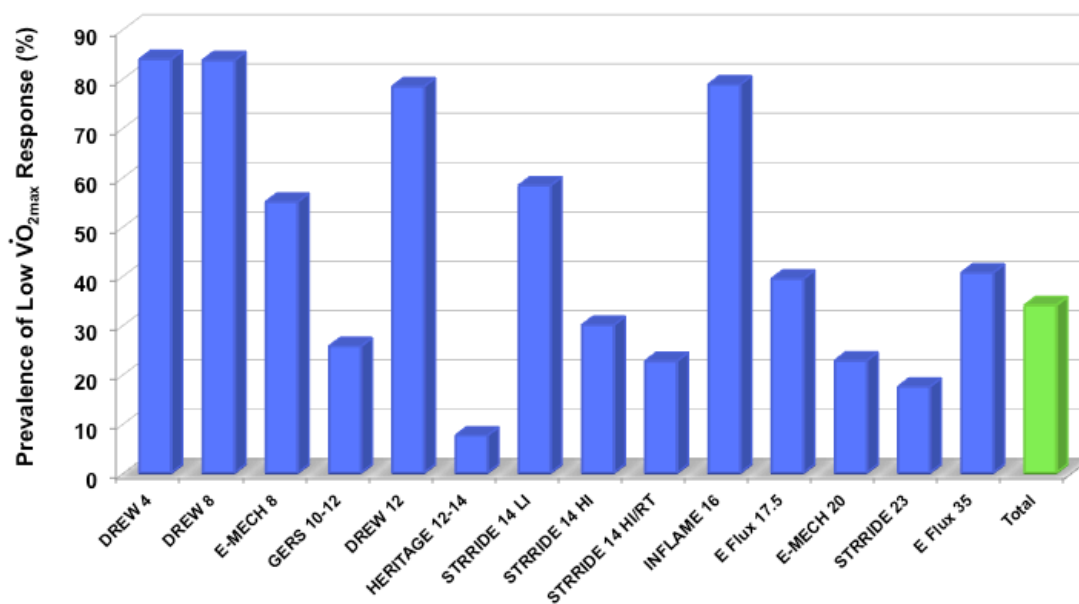


Figure 5.2a. Prevalence of low $\dot{V}O_{2\max}$ response based on absolute terms for each exercise intervention ordered by increasing dose of exercise ($\text{kcal} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$; KKW)

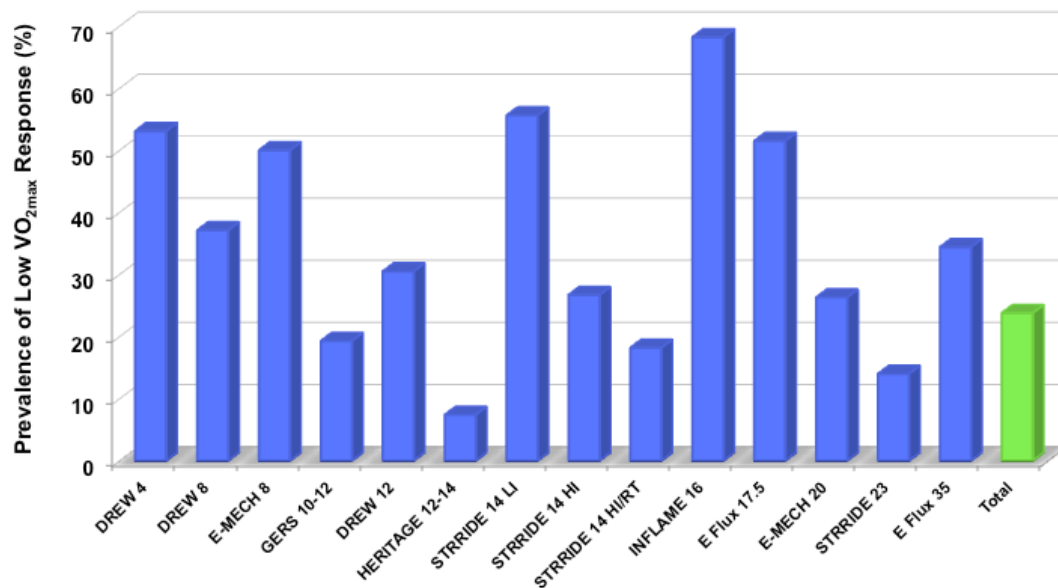


Figure 5.2b. Prevalence of low $\dot{V}O_{2max}$ response based on relative terms for each exercise intervention ordered by increasing dose of exercise ($\text{kcal}\cdot\text{kg}^{-1}\cdot\text{week}^{-1}$; KKW)

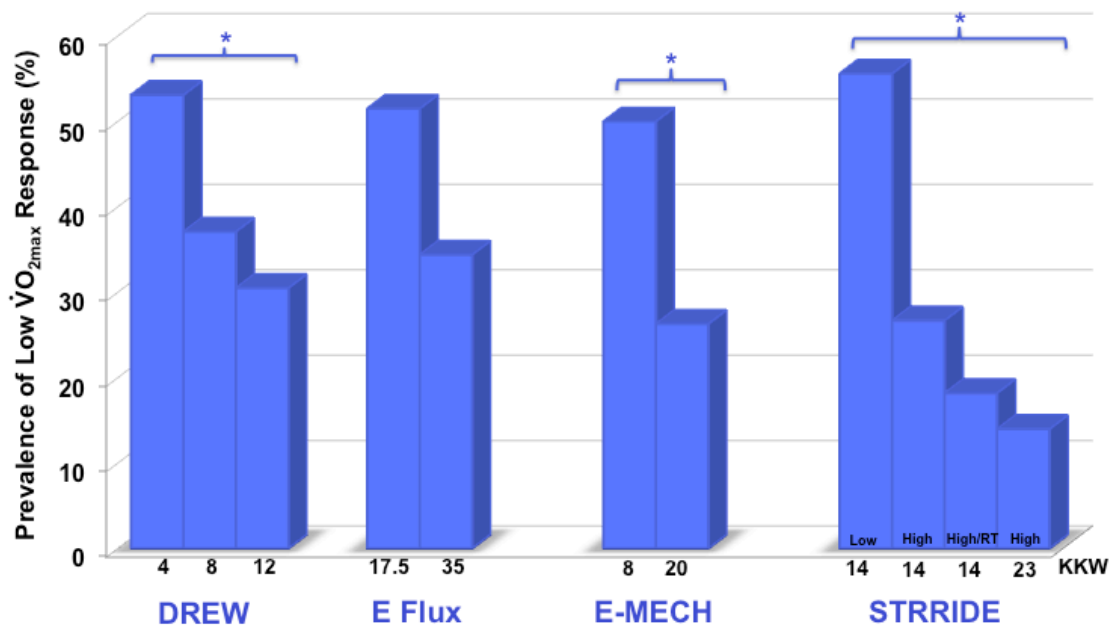


Figure 5.3. Prevalence of low $\dot{V}O_{2max}$ response based on relative terms for studies employing multiple exercise interventions ordered by increasing dose of exercise ($\text{kcal}\cdot\text{kg}^{-1}\cdot\text{week}^{-1}$; KKW); *indicates statistically different between intervention groups ($p < 0.01$)

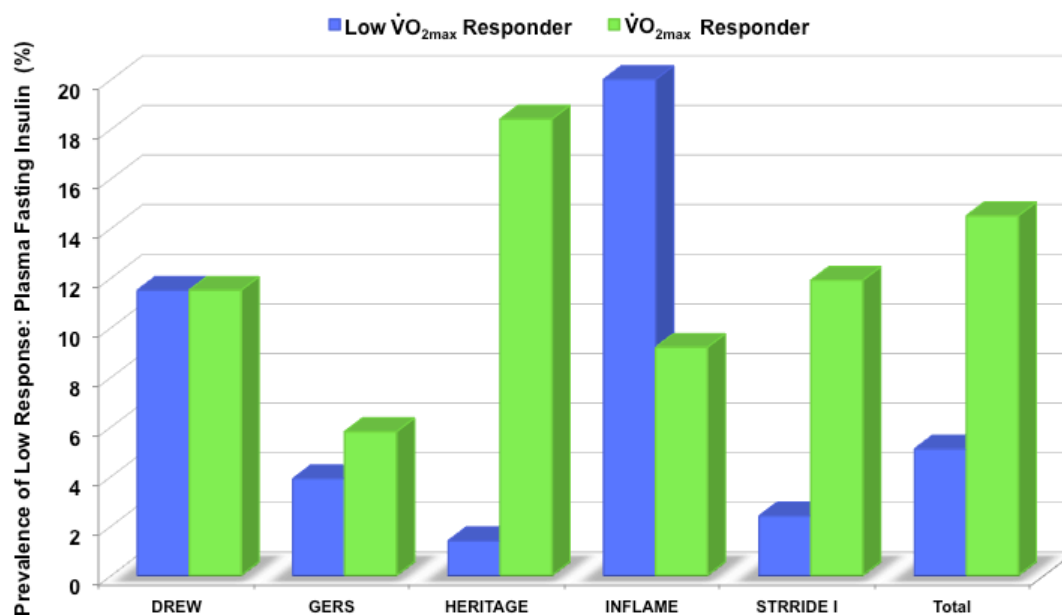


Figure 5.4a. Prevalence of low response for plasma fasting insulin across studies by relative $\dot{V}O_{2max}$ groups

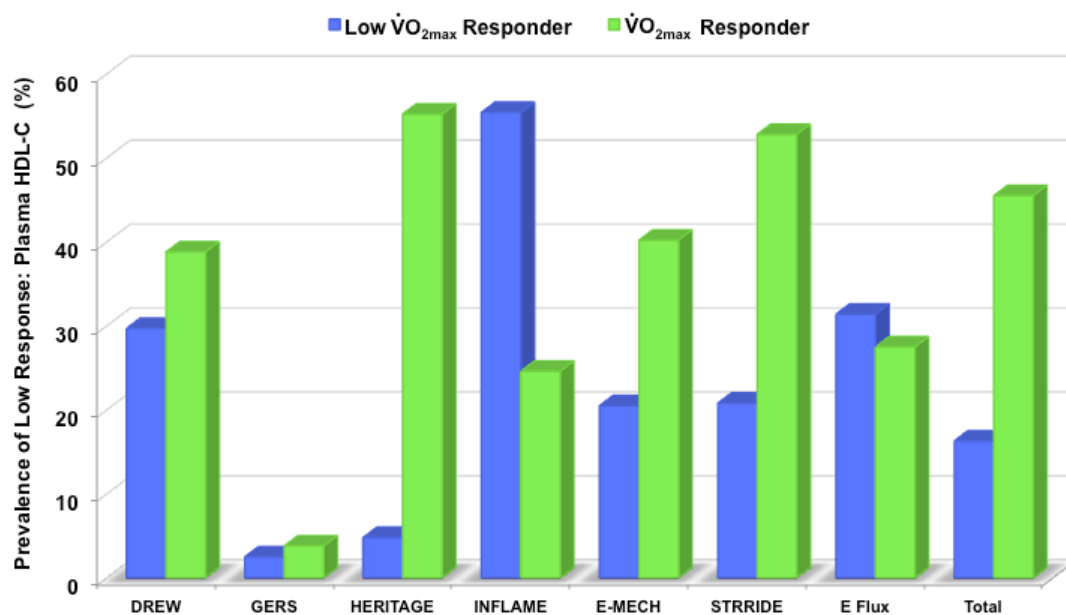


Figure 5.4b. Prevalence of low response for plasma HDL-C across exercise by relative $\dot{V}O_{2max}$ groups

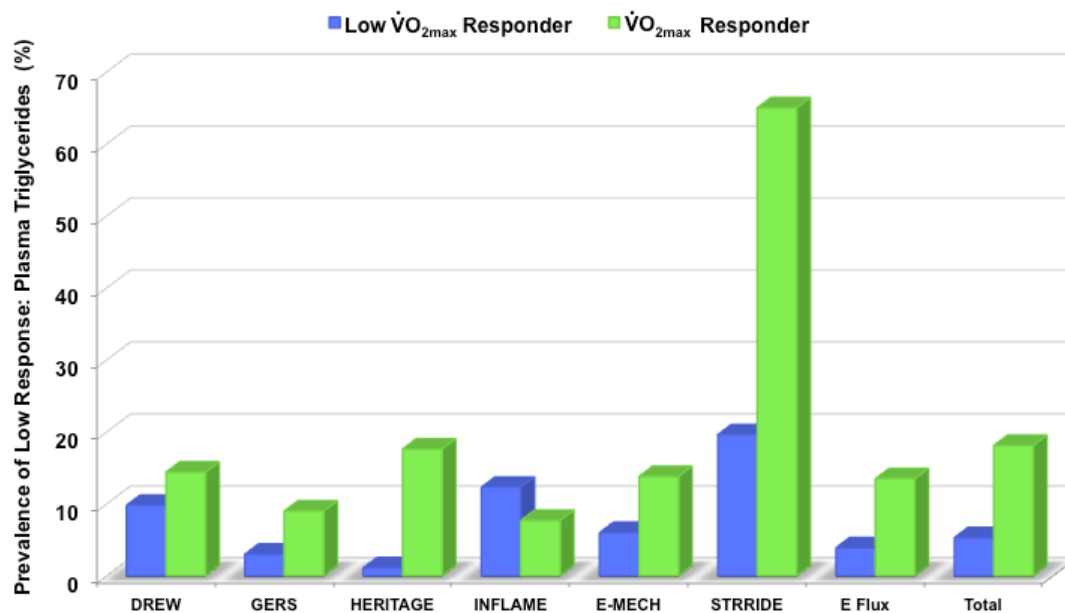


Figure 5.4c. Prevalence of low response for plasma triglycerides across studies by relative $\dot{V}O_{2max}$ groups

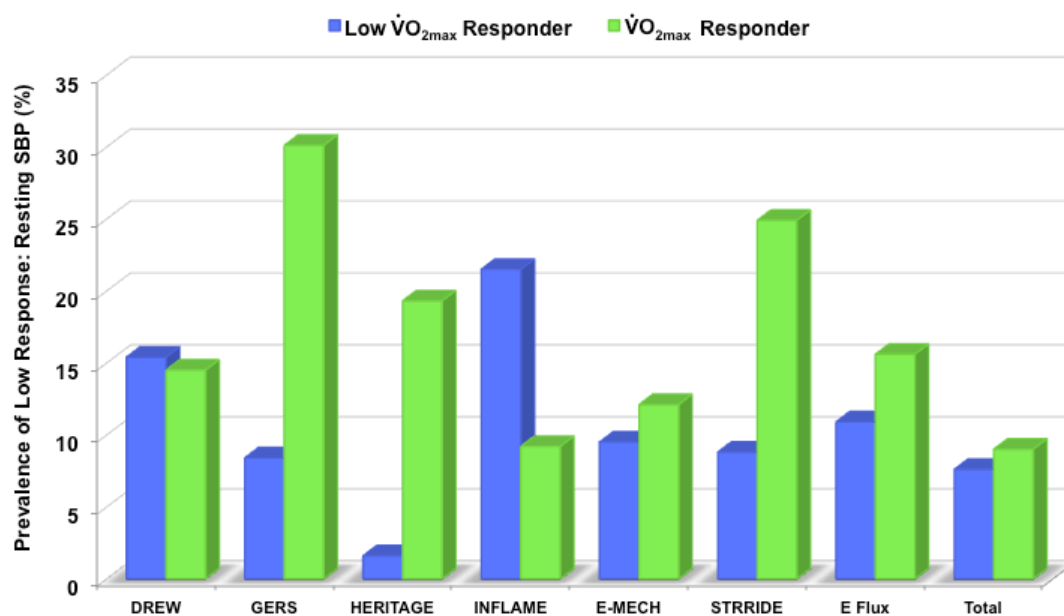


Figure 5.4d. Prevalence of low response for resting systolic blood pressure across studies by relative $\dot{V}O_{2max}$ groups

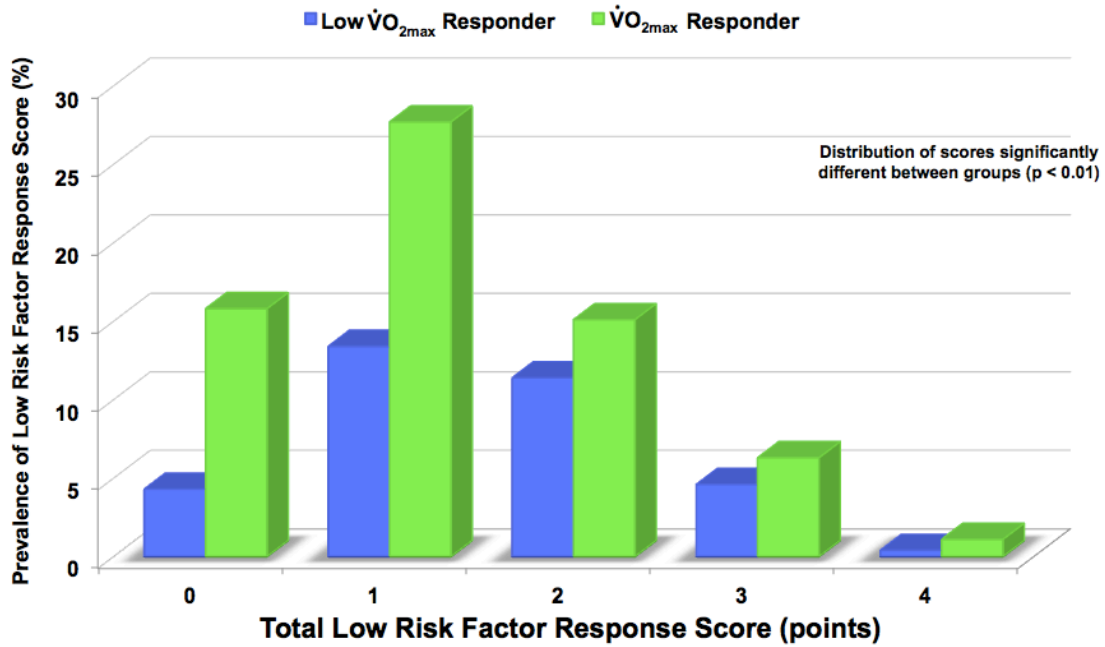


Figure 5.5a. Distribution of risk factor response score for all exercisers (n=1,081) by absolute $\dot{V}O_{2max}$ groups

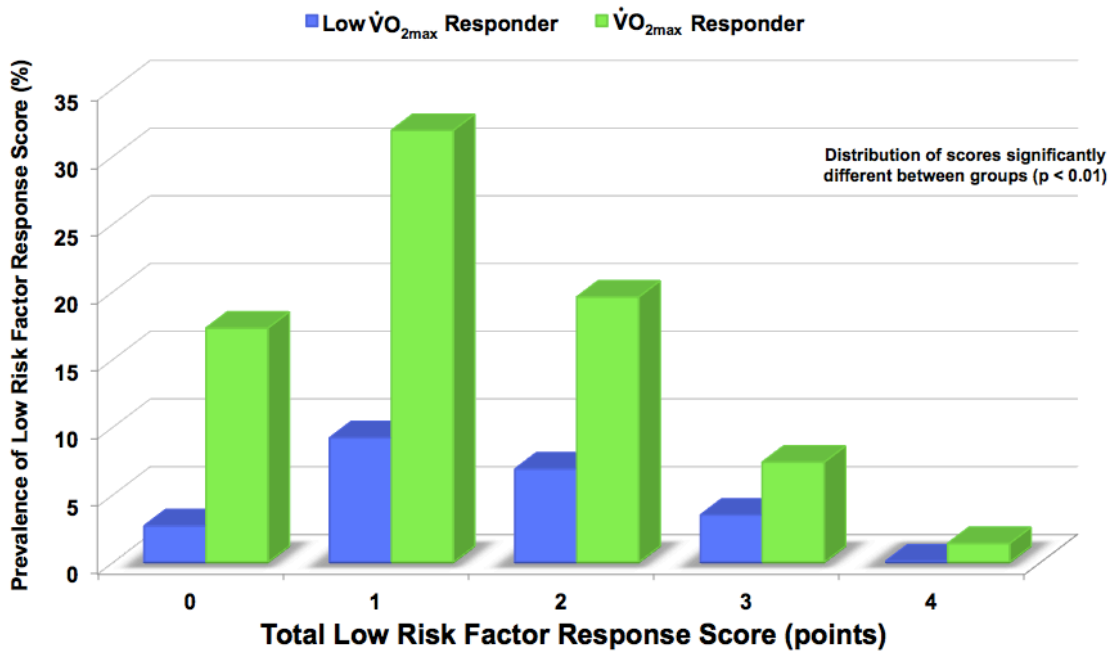


Figure 5.5b. Distribution of risk factor response score for all exercisers (n=1,081) by relative $\dot{V}O_{2max}$ groups

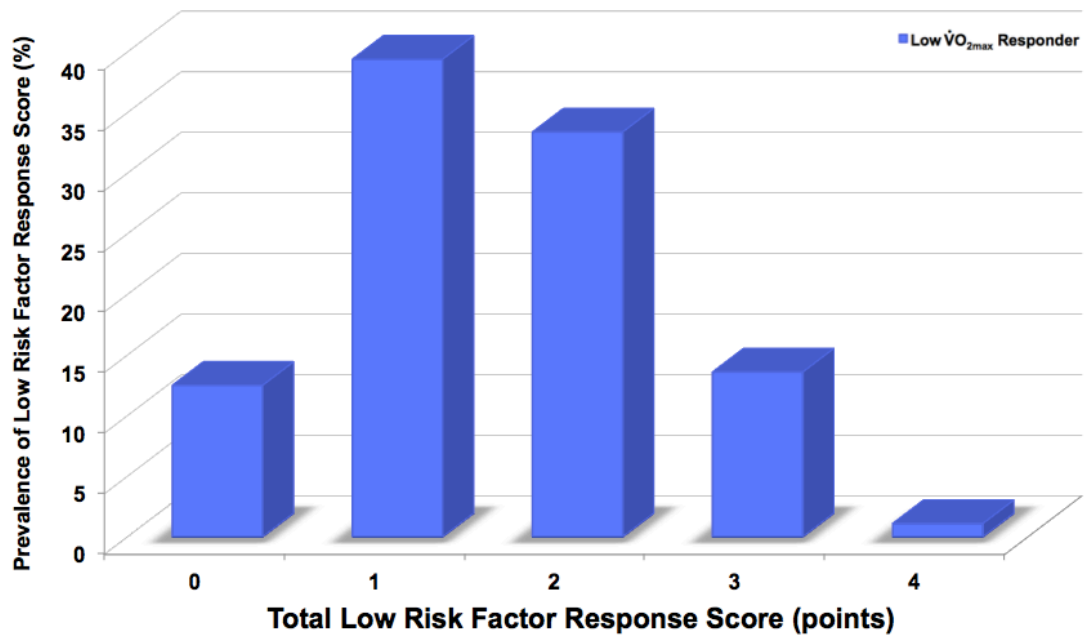


Figure 5.6a. Distribution of risk factor response score amongst absolute low $\dot{V}O_{2\max}$ responders (n=241)

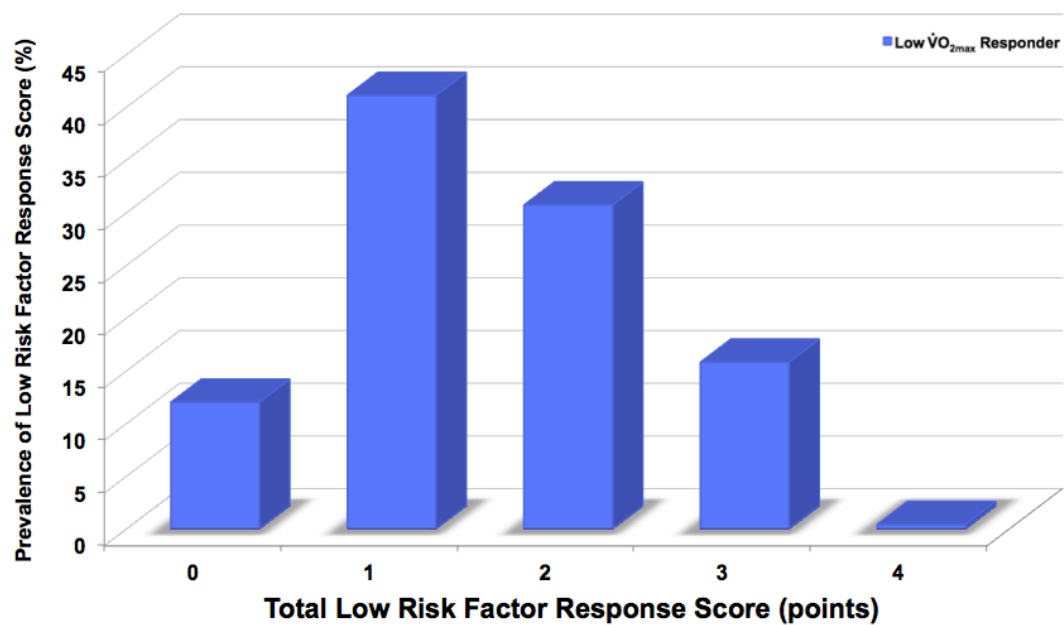


Figure 5.6b. Distribution of risk factor response score amongst relative low $\dot{V}O_{2\max}$ responders (n=241)

CHAPTER 6

OVERALL DISCUSSION

Purpose

The purposes of this dissertation were to: 1) evaluate whether ideal CVH is associated with CRF 2) examine the relationship between changes in CRF and changes in ideal CVH score over time, 3) assess the prevalence of low $\dot{V}O_{2\max}$ response following aerobic exercise intervention, and 4) investigate the relationship between $\dot{V}O_{2\max}$ responsiveness and training-induced changes in cardiometabolic risk factors following aerobic exercise intervention.

Methods

The first study examined the cross-sectional relationship between CRF and ideal CVH score ($n=11,590$), as well as the longitudinal relationship between changes in CRF and changes in ideal CVH score over time ($n=2,555$) in middle-aged men and women from the ACLS. Participants underwent thorough medical examination at baseline and follow-up at the Cooper Clinic in Dallas, TX. CRF was measured as duration in minutes from a maximal treadmill test. Ideal CVH score was calculated on a 14-point scale using data on LS7 metrics. Participants were grouped into categories of inadequate (0-4), average (5-9), and optimum (10-14) based on their CVH score. Three CRF groups were created based on previously established cutpoints of treadmill time: low, moderate, and high CRF. For longitudinal analyses, participants ($n=2,555$ who had at least two clinic visits)

were grouped into categories of loss, stable, or gain, by change in CRF and change in ideal CVH score.

The second study investigated the responsiveness of $\dot{V}O_{2\max}$ and select cardiometabolic risk factors following aerobic exercise intervention. The prevalence of low $\dot{V}O_{2\max}$ response was examined in 1,724 previously sedentary adults who completed one of 14 exercise interventions. The interventions ranged from doses of 4-35 KKW; intensities of 50-85% $\dot{V}O_{2\max}$; and durations of 20-35 weeks. All participants underwent multiple laboratory measures at baseline and post-training. $\dot{V}O_{2\max}$ was assessed via graded maximal exercise testing with gas exchange. Blood pressure was measured after participants sat quietly for at least five minutes. Blood samples were obtained from venipuncture of an antecubital vein in the morning following an overnight fast. Blood samples were analyzed for plasma fasting insulin, HDL-C, and TG concentrations. Post-training blood samples were obtained approximately 16-72 hours after the completion of the final exercise session. For each of these traits, change (Δ) was calculated as the post-training value minus the baseline value.

Low $\dot{V}O_{2\max}$ response was defined in both absolute (gain <120 ml/min from baseline value) and relative (gain <5% of study-specific baseline average $\dot{V}O_{2\max}$ in mL·kg⁻¹·min⁻¹) terms.. For the select cardiometabolic risk factors, any value beyond 1xTE in a direction indicating a worsening of the risk factor was considered a low response. The threshold values to assess low response were: Δ plasma fasting insulin ≥ 12 pmol/L; Δ plasma HDL-C ≤ 0.12 mmol/L; Δ plasma TG ≥ 0.21 mmol/L; and Δ resting SBP ≥ 5 mmHg.

Main Findings

One of the main findings from the first study was that higher levels of CRF are strongly associated with better CVH profiles, which is demonstrated by moderate and high fit individuals having almost 11 and 40 times greater odds of having average or optimum CVH, respectively, compared to low fit individuals. In addition, longitudinal analyses showed that improvements in CRF over time are independently associated with concomitant increases in CVH scores and these increases in CRF explained a greater amount of variance in CVH score compared to each of the individual LS7 metrics (blood cholesterol, fasting plasma glucose, BP, smoking, BMI, diet quality, and PA).

The second study found a high prevalence of $\dot{V}O_{2\max}$ low response across 14 diverse exercise interventions, which differed based on how low response was defined (34% relative; 24% relative). The prevalence of low response for the select cardiometabolic risk factors varied from 19.6% for changes in fasting insulin to 61.7% for changes in HDL-C. Despite the high prevalence of low response observed across all studies, the likelihood of being a low responder for all traits ($\dot{V}O_{2\max}$, fasting insulin, HDL-C, TG, and SBP) was extremely low, as only one participant out of 1,081 (0.1%) did not demonstrate exercise training-induced changes below the low response threshold for these traits.

Conclusions

Results from this dissertation support the vital role CRF plays in public health efforts aiming to prevent the development of CVD and promote the achievement and maintenance of ideal CVH. Although substantial inter-individual

variation in response to regular exercise exists, results from this dissertation also show that regular exercise participation is associated with many health benefits, regardless of the presence of a detectable $\dot{V}O_{2\max}$ response. Future research can build upon these findings to refine the identification of individuals who respond unfavorably to regular exercise and to subsequently adjust their exercise prescription. This will enhance our ability to utilize exercise as medicine and provide appropriate guidance to improve health and attenuate risk for CVD.

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